Critical Parameters in Selecting a Neuromuscular Blocking Agent

	Norcuron® (vecuronium bromide) for injection	**atracurium besylate**
HEMODYNAMICS	Virtually free of cardiovascular side effects, even at higher doses (0.28 mg/kg)[1]	Significant variations in blood pressure and cardiac output[2]
HISTAMINE	Histamine release unlikely even at 0.28 mg/kg	Precaution advised for patients in whom substantial histamine release would be hazardous (clinically significant cardiovascular disease, asthma)[3]
DURATION OF ACTION	Shorter-acting at equipotent doses[4]	Significantly slower recovery[4]
DOSING FLEXIBILITY	Can be used in short, intermediate, or long cases. No dosage adjustments required to avoid cardiovascular side effects[5]	Doses higher than 0.5 mg/kg not recommended.[3] Dosage adjustments needed to avoid histamine release[3,6]
STORAGE	Room temperature	Constant refrigeration[3]
STABILITY	2-year shelf life in lyophilized form	2-year shelf life (under refrigeration) immediately reduced to 14 days once removed from refrigeration, even if re-refrigerated[3]

Norcuron®

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

- 0.9% NaCl solution
- 5% glucose in water
- Sterile water for injection
- 5% glucose in saline
- Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

References:

1. Morris RB, Cahalan MK, Miller RD, Wilkinson PL, Quasha AL, Robinson SL. The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology*. 1983;58:438–440.
2. Gallo JA, Cork RC, Puchi P. Comparison of effects of atracurium and vecuronium in cardiac surgical patients. *Anesth Analg*. 1988;67:161–165.
3. Tracrium* Injection (atracurium besylate) package insert.
4. Bailey DM, Nicholas ADG. Comparison of atracurium and vecuronium during anaesthesia for laparoscopy. *Br J Anaesth*. 1988;61:557–559.
5. Feldman SA. Vecuronium — A variable dose technique. *Anaesthesia*. 1987;42:199–201.
6. Scott RPF, Savarese JJ, Basta SJ, et al. Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response. *Br J Anaesth*. 1985;57:550–553.

*Tracrium is a registered trademark of Burroughs Wellcome Co.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Manufactured for ORGANON INC.
By BEN VENUE LABORATORIES, INC. • BEDFORD, OHIO 44146
or by
ORGANON INC. • WEST ORANGE, NEW JERSEY 07052

© 1990 ORGANON INC. ORG-11261 PRINTED IN USA NOVEMBER 1990 cu6-H02985-39-P02451

Anesthesia and Analgesia

Journal of International Anesthesia Research Society

Suite 140, 2 Summit Park Drive, Cleveland, Ohio 44131-2553 Telephone: (216) 642-1124

Editorial Board

Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada
Phillip O. Bridenbaugh, MD, Cincinnati, Ohio
Mieczyslaw Finster, MD, New York, New York
Thomas J. Gal, MD, Charlottesville, Virginia
Paul R. Hickey, MD, Boston, Massachusetts
Edward D. Miller, Jr, MD, New York, New York
Walter S. Nimmo, MD, BSc, FRCP, FFARCS, Sheffield, United Kingdom
Nathan L. Pace, MD, Salt Lake City, Utah
Richard J. Palahniuk, MD, Minneapolis, Minnesota
Ronald G. Pearl, MD, PhD, Stanford, California
Donald S. Prough, MD, Winston-Salem, North Carolina
Joseph G. Reves, MD, Durham, North Carolina
John J. Savarese, MD, New York, New York
John H. Tinker, MD, Iowa City, Iowa
Barbara E. Waud, MD, Worcester, Massachusetts

Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: ICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale niversity School of Medicine, 333 Cedar Street, New Haven, CT 06510 elephone: 203-785-4703). For information concerning preparation of manuripts see "A Guide for Authors" published quarterly in the Journal.

Books for review should be sent directly to the Book Review Editor, ORIG ELLISON, MD, Department of Anesthesia, University of Pennsylnia, Philadelphia, PA 19104.

Reprints: For single copies, write directly to the senior author at the dress listed on the title page. Quantity orders (minimum 100) processed ough ELSEVIER SCIENCE PUBLISHING CO, INC, 655 Avenue of the mericas, New York, NY 10010; prices on request.

All articles published in this Journal become the property of the Internaonal Anesthesia Research Society. This journal has been registered with the opyright Clearance Center, Inc. Consent is given for the copying of articles or personal or internal use, or for the personal or internal use of specific lients. This consent is given on the condition that the copier pay through he Center the per-copy fee stated in the code on the first page of each article or copying beyond that permitted by the US Copyright Law. If no code ppears on an article, the author has not given broad consent to copy, and ermission to copy must be obtained directly from the author. This consent oes not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works.

On-line text is available through BRS Colleague, 8000 Westpark Drive, McLean, VA 22102; telephone (800) 289-4277.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, Edward D. Miller, Jr, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K. C. Wong, MD, PhD. Emeritus Trustees are: Paul R. Dumke, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Morris J. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1991 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year, in all other countries $110.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited by anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, and students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: International Anesthesia Research Society, Suite 140, 2 Summit Park Drive, Cleveland, Ohio 44131-2553.

Subscription information for 1991 applying to non-IARS members: Institutions, $140.00; nonmember individuals, $100.00. Outside of the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico, $55.00 for surface airlift to Europe, $75.00 for surface airlift to Japan, and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

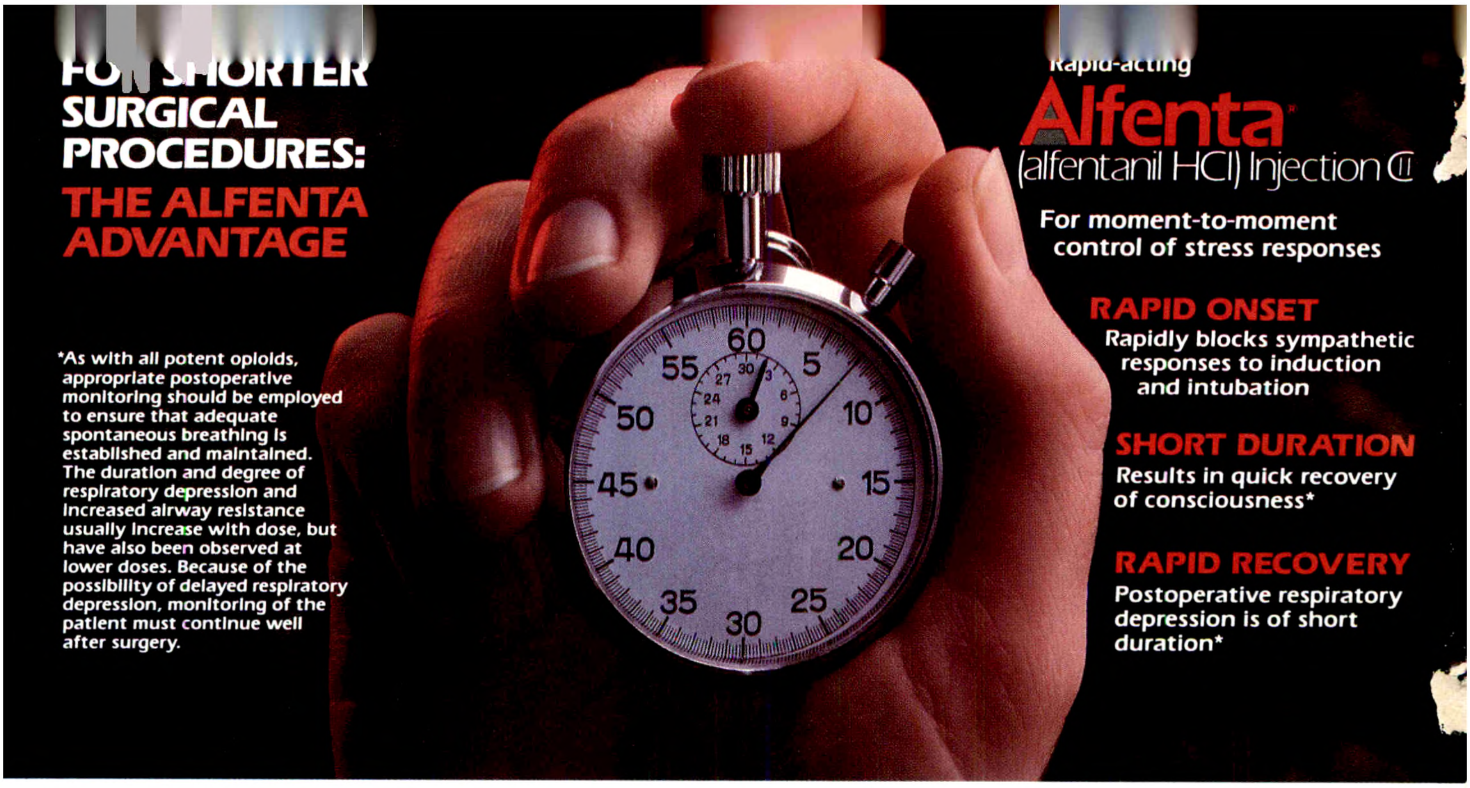
Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical sciences, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

This journal is printed on acid-free paper.



*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 μg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	[illegible]
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	[illegible]
Skeletal Muscle Movements	6	2	6	2	0	[illegible]
Respiratory						
Apnea	7	0	0	0	0	[illegible]
Postoperative Respiratory Depression	2	2	0	0	0	[illegible]
CNS						
Dizziness	3	5	0	0	0	[illegible]
Sleepiness/ Postoperative Sedation	2	8	2	0	0	[illegible]
Blurred Vision	2	2	0	0	0	[illegible]

*From two clinical trials, one involving supplemented balanced barbiturate/nitrous oxide anesthesia and healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchosp postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urti itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled dru that can produce drug dependence of the morphine type and therefore has the potential for being abuse
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFEN (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No e overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0- in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenc tration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage res depression. The duration of respiratory depression following overdosage with ALFENTA may be longer tha duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude imn establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indica hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular b agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive age be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individua each patient according to body weight, physical status, underlying pathological condition, use of other dru type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal tota weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFE should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored r Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. for

JANSSEN
PHARMACEUTICA
Piscataway, N.J. 08854

March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

© Janssen Pharmaceutica Inc. 1989 JPI-AL-040A

Anesthesia and Analgesia

Contents

Volume 72, Number 1, January 1991

EDITORIAL

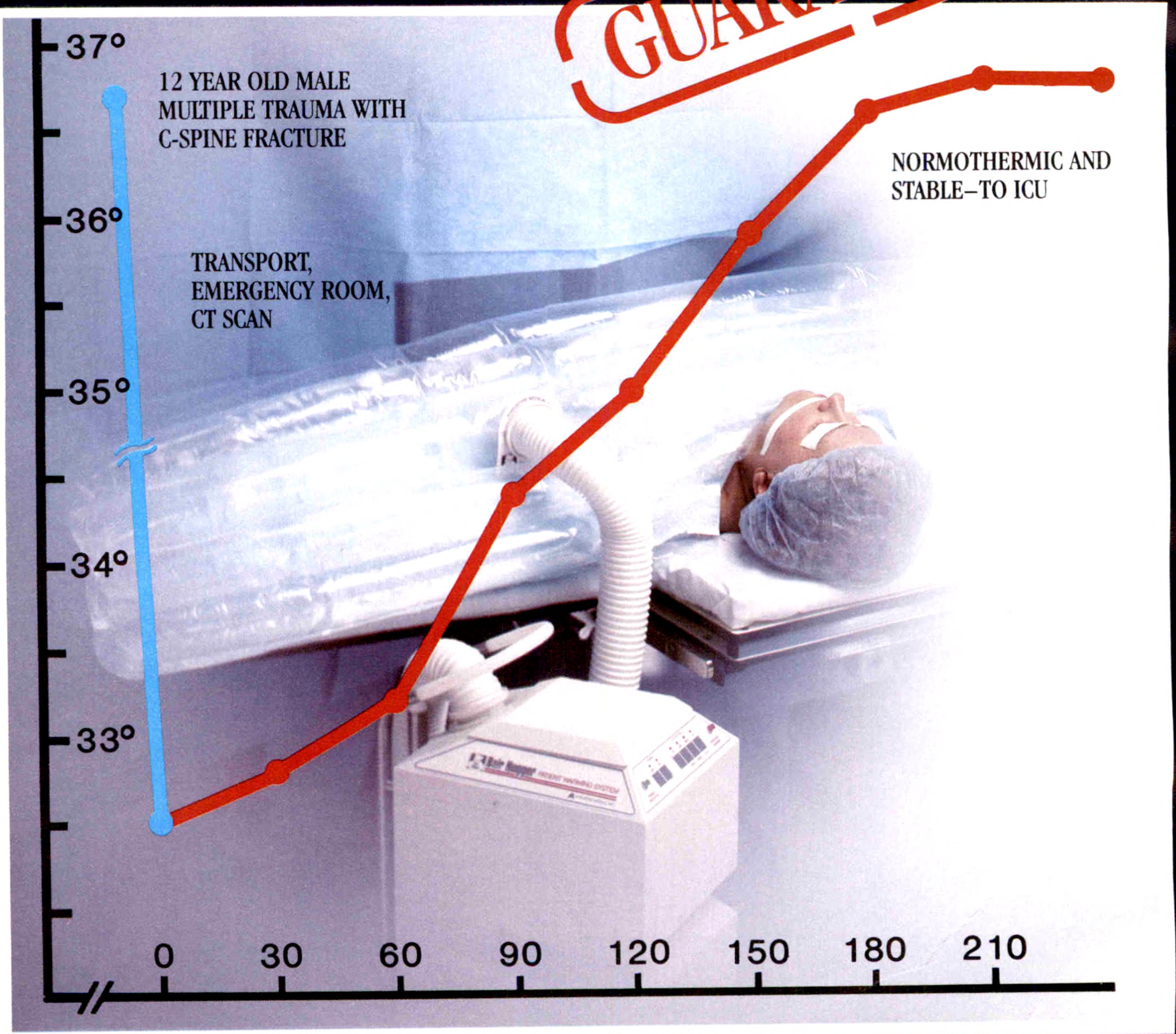
Halothane, Catecholamines, and Cardiac Conduction: Anything New?	*Zeljko J. Bosnjak and Lawrence A. Turner*	1

SCIENTIFIC ARTICLES

Effects of Halothane on Impulse Propagation in Purkinje Fibers and at Purkinje-Muscle Junctions: Relationship of V_{max} to Conduction Velocity	*Lisa C. Freeman and William W. Muir III*	5
α-Adrenoceptor Stimulation in the Presence of Halothane: Effects on Impulse Propagation in Cardiac Purkinje Fibers	*Lisa C. Freeman and William W. Muir III*	11
Nitrous Oxide Potentiates Succinylcholine Neuromuscular Blockade in Humans	*James E. Szalados, François Donati, and David R. Bevan*	18
Steal-Prone Coronary Anatomy and Myocardial Ischemia Associated With Four Primary Anesthetic Agents in Humans	*Stephen Slogoff, Arthur S. Keats, Wayne E. Dear, Antonio Abadia, James T. Lawyer, J. Patrick Moulds, and Timothy M. Williams*	22
Cardiodynamic Effects of Propofol in Comparison With Thiopental: Assessment With a Transesophageal Echocardiographic Approach	*Jan P. Mulier, Patrick F. Wouters, Hugo Van Aken, Gery Vermaut, and Eugène Vandermeersch*	28
A Blinded Comparison of Noninvasive, In Vivo Phosphorus Nuclear Magnetic Resonance Spectroscopy and the In Vitro Halothane/Caffeine Contracture Test in the Evaluation of Malignant Hyperthermia Susceptibility	*Jeffrey Olgin, Henry Rosenberg, Gregory Allen, Richard Seestedt, and Britton Chance*	36
Cerebral Blood Flow Autoregulation Is Preserved During Cardiopulmonary Bypass in Isoflurane-Anesthetized Patients	*L. John Aladj, Narda Croughwell, L. R. Smith, and J. G. Reves*	48
Epidural Morphine With Butorphanol for Postoperative Analgesia After Cesarean Delivery	*C. D. Lawhorn, J. D. McNitt, E. E. Fibuch, J. T. Joyce, and R. J. Leadley, Jr*	53
Efficacy of Ephedrine in the Prevention of Postoperative Nausea and Vomiting	*David M. Rothenberg, Samuel M. Parnass, Kim Litwack, Robert J. McCarthy, and L. Michael Newman*	58
Electrophysiologic Effects of Bupivacaine in the Isolated Rabbit Heart	*Pierre Lacombe, Gilbert Blaise, Didier Loulmet, and Charleen Hollmann*	62
Isoproterenol Corrects the Effects of Bupivacaine on the Electrophysiologic Properties of the Isolated Rabbit Heart	*Pierre Lacombe, Gilbert Blaise, Charleen Hollmann, Mario Tanguay, and Didier Loulmet*	70

NORMOTHERMIA IN THE O.R.

GUARANTEED*



TIME IN SURGERY

BAIR HUGGER™
CONVECTIVE WARMING™
THERAPY STARTED

*Terms of guarantee:

1. Bair Hugger™ Convective Warming Therapy must begin immediately after induction of anesthesia on the "high" setting and continue throughout the case if indicated.

2. Infused blood and fluids must be warmed to body temperature.

If these two criteria are met and the patient is hypothermic at the end of the operation (core temperature <36°C), Augustine Medical will replace the Warming Cover. This guarantee is limited to the replacement of the Warming Cover.

Bair Hugger™

For more information about Bair Hugger™ Convective Warming Therapy, call 1-800-733-7775 or (612) 941-8866

AUGUSTINE MEDICAL INC.
PRACTICAL SOLUTIONS TO COMMON PROBLEMS IN ACUTE CARE™
10393 West 70th Street • Eden Prairie, Minnesota 55344

SCIENTIFIC ARTICLES—*continued*

Cerebral Effects of Nitrous Oxide When Added to Low and High Concentrations of Isoflurane in the Dog — *Ole Kristian Roald, Marianne Forsman, Mona S. Heier, and Petter A. Steen* 75

Effective Doses of Epidural Morphine for Relief of Postcholecystectomy Pain — *Hiroshi Yamaguchi, Seiji Watanabe, Izumi Harukuni, and Yoshihiro Hamaya* 80

Pretreatment With *d*-Tubocurarine, Vecuronium, and Pancuronium Attenuates Succinylcholine-Induced Increases in Plasma Norepinephrine Concentrations in Humans — *Shuzo Oshita, Sadahei Denda, Yoshiki Fujiwara, Hiroshi Takeshita, and Futami Kosaka* 84

Effect of Obesity on Safe Duration of Apnea in Anesthetized Humans — *Holly G. Jense, Stevin A. Dubin, Paul I. Silverstein, and Una O'Leary-Escolas* 89

Clinical Evaluation of Autotransfusion During Liver Transplantation — *Yoogoo Kang, Shushma Aggarwal, Mohamed Virji, A. William Pasculle, Jessica H. Lewis, Judith A. Freeman, and Lisa K. Martin* 94

Amino Acids Fail to Prevent Halothane Depression of Albumin Synthesis: Studies in the Isolated Perfused Rat Liver — *Jonathan B. Kruskal, John J. Franks, and Ralph E. Kirsch* 101

Interpleural Analgesia After Thoracotomy — *F. Michael Ferrante, Vincent W. S. Chan, G. Richard Arthur, and Angelo G. Rocco* 105

Comparison of Vecuronium- and Atracurium-Induced Neuromuscular Blockade in Postpartum and Nonpregnant Patients — *Karin S. Khuenl-Brady, Johann Koller, Peter Mair, Friedrich Pühringer, and Gottfried Mitterschiffthaler* 110

Effects of Hydralazine and Prostaglandin E_1 on Regional Myocardial Function in the Ischemic Canine Heart — *Shigeho Morita, Hisato Takahashi, Masashi Kono, Yukihiko Uno, Midori Ozawa, and Toshiro Sato* 114

CLINICAL REPORTS

Caudal Morphine for Postoperative Analgesia in Infants and Children: A Report of 138 Cases — *Robert D. Valley and Ann G. Bailey* 120

Too Much of a Good Thing: Uvular Trauma Caused by Overzealous Suctioning — *Martin S. Bogetz, Bradley J. Tupper, and A. Christopher Vigil* 125

LETTERS TO THE EDITOR

Correct Application of the Shunt Fraction Calculation — *Julio C. Cruz and Patricia J. Metting* 127

In Response — *Michael E. Goldberg, Joaquin Cantillo, Marc Torjman, Stephen McNulty, and Said S. Azad* 127

ECG Signals During Cardiopulmonary Bypass: Artifacts or Reality? — *Bruce Kleinman, Kamlesh Shah, and Uday Jain* 128

In Response — *Hoshang J. Khambatta, J. Gilbert Stone, and Alvin Wald* 129

When you just can't wait for a helping hand.

Because the Arrow® Hands-Off™[1] PA catheter is completely encased in sterile protection, you can test, flush, and prepare it single-handedly with virtually no risk of contamination.

Only Arrow® Hands-Off™ PA catheters protect against external contamination during placement and withdrawal. This protection comes from the total encapsulation of the catheter within an integral Arrow® Cath-Gard®[2] contamination shield and flushing balloon test chamber.

Exposure to blood-borne diseases becomes less of a worry. And, when required, you can place the catheter without an assistant–important to know in emergency situations.

Now available with temporary transvenous pacing capability.

The Arrow® Thermo-Pace™ Hands-Off™* model lets you achieve temporary transvenous pacing as you obtain hemodynamic pressures and measure cardiac outputs–all under aseptic conditions.

Like all Hands-Off™ catheters, its torque-control material makes manipulation easier. The unique CathLok™ hub[3] (left) firmly grips the catheter and inhibits movement once the catheter is in place. Centimeter markings aid in proper placement. And color-coded, translucent, insert-molded polyurethane extension lines with clamps help to differentiate lines.

For maximum contamination protection and resistance to catheter kinking, Hands-Off™ catheters are designed to be placed with Arrow-Flex® Percutaneous Sheath Introducers.

Why place your patients–and yourself–at unnecessary contamination risk? Ask your Arrow representative, or call, about the free procedural videotape library and complete Hands-Off™ product information. Give yourself and your patients all the security that Arrow leadership can deliver.

Targeting your clinical needs and cost realities.

ARROW®
INTERNATIONAL, INC.

U.S.A.
Arrow International, Inc., Hill and George Avenues, Reading, PA 19610.
Phone: 215 378-0131. Call toll-free 800 523-8446. Orders-only toll-free Fax: 800 343-2935.
Fax: 215 374-5360.

Canada
Arrow Medical Products, Ltd., 150 Britannia Road East, Unit #20, Mississauga, Ontario
L4Z 1S6. Call toll-free 800 387-7819 or in Toronto 416 890-0173.

Europe
Arrow International, Inc. (Europe), P.O. Box 345, Pampuslaan 1, 1380 A H Weesp,
The Netherlands. Phone: (0)2940-80258, Fax: (0)2159-48471.

Arrow Deutschland, G.m.b.H., Otto Hahn-Strasse 4, 8058 Erding, West Germany.
Phone: (0)8122-3026, Fax: (0)8122-40384.

Japan
Arrow Japan, Ltd., 9F Chiyoda Asahi Building, 2-8-3 Iidabashi, Chiyodaku, Tokyo 102.
Phone: 03-222-5496, Fax: 03-222-5396.

Arrow Japan, Ltd., Shin-Osaka Kita Bldg. 4F, 1–46 Miyahara 4-chome, Yodogawa-ku,
Osaka 532, Japan. Phone: 06-397-7070, Fax: 06-397-7575.

[1,3] Patent pending.

[2] U.S. Patent Number 4,327,723.
Canadian Patent Number 4,515,592.

*Refer to product labeling for information about pacing electrodes compatible with Arrow® Thermo-Pace™ Hands-Off™ catheters, or contact Arrow International, Inc.

Refer to package insert for current warnings, precautions, and instructions for use.

©1990, **Arrow International, Inc.**

LETTERS TO THE EDITOR—*continued*

Epidural Blood Patch: Why the Rapid Response? *Len E. S. Carrie* 129

A Modest Proposal for Improved Humidifier Design *Eric L. Shampaine and Mark Helfaer* 130

BOOK REVIEWS

Lectures on Anesthetics and on Asphyxia by Claude Bernard. Translated by B. Raymond Fink *A. Michael Broennle* 132

Problems in Anesthesia: Thoracic Anesthesia by J. B. Brodsky, guest ed. *P. D. Slinger* 132

Emergency Airway Management by Michael S. Gorback, ed. *William E. Hurford* 133

Outpatient Anesthesia by Paul F. White, ed. *Barbara S. Gold* 133

Clinical Monitoring by Carol L. Lake *Lawrence C. Siegel* 134

Anesthesiology and Vascular Surgery, Perioperative Management of the Vascular Surgical Patient by Mark P. Yeager and David Glass, eds. *John A. Youngberg* 134

Regional Anesthesia for Intraocular Surgery by K. Zahl and M. A. Meltzer, eds. *John J. Leahey* 135

Books Received 135

A Guide for Authors A31

Are patients' drugs of choice... going to affect your drugs of choice?

Anesthetics can interact with many illegal drugs, causing arrhythmias and other complications.[1]
Always ask about drug abuse in your presurgical interview.
And be prepared for possible complications of drug abuse in trauma patients.
Or your patients may have no choices left.

1. Rowbotham MC: Neurologic aspects of cocaine abuse (Medical Staff Conference). *West J Med* 1988;149:442-448.

Partnership for a Drug-Free America

IARS MEMBERSHIP

FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a nonprofit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end, the IARS

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March

Funds projects in anesthesia-related research, clinical care, education, and administration through the B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, or national anesthesia organization. Membership is open to individuals who qualify in the various categories shown below. All memberships include a monthly subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee. Only IARS members may apply for the B.B. Sankey Anesthesia Advancement Award.

MEMBERSHIP CATEGORIES

MEMBERSHIP: Open to individuals with doctorate degrees who are licensed to practice in the medical, osteopathic, dental, or veterinary medicine fields (i.e., MD, MB, DO, DDS, DVM); and to individuals with doctorate degrees (PhD) in any scientific discipline who are engaged in academic, private, or commercial research.

ASSOCIATE MEMBERSHIP: Open to individuals in the allied health professions who are certified by their professional accrediting organization as nurse anesthetists (CRNA), respiratory therapists or technicians (RRT or CRTT), physician assistants (PA, MMS), and other allied health professionals in anesthesia-related practice.

Annual (1991 Calendar Year) Dues for Members and Associate Members: $90 ($110 foreign).

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists, or technicians.

Annual Dues for Educational Members: One-half of the member rate. These memberships are entered in January or July for 2-, 3-, or 4-year periods. Official application, certified by program directors, must be used and submitted with check to cover full membership period.

International Anesthesia Research Society
Suite 140-2 Summit Park Drive, Cleveland, Ohio 44131-2553

Please send me_______application(s) for:

❒ Membership ❒ Associate Membership ❒ Educational Membership

Please print clearly:____
Name and Degree / Certification

____
Street Address City, State, Zip Code (country)

The Osler Institute

Anesthesiology Boards Review Course

February 9-15, 1991 – Las Vegas

§April 15-20, 1991 – San Diego July 6-11, 1991 – Chicago

Now offering §60 hours of mock oral exams limited to 90 participants

OBJECTIVES

After this program attendees should:

- Have improved basic and clinical anesthesia knowledge
- Be better organized for further study of anesthesiology
- Be prepared to take written and oral exams

METHODS

- HOME STUDY MATERIALS consisting of a syllabus and assignments with questions and answers
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

§ Plus optional extra mock oral exam days April 21-23, 1991

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

PHYSIOLOGY
- Respiratory Physiology
- Cardiovascular Physiology
- Neurophysiology
- Hepatic Physiology
- Renal Physiology
- Acid-Base and Blood Gas
- Endocrine Physiology
- Thermoregulation

PHARMACOLOGY
- Pharmacokinetics
- Inhalation Anesthetics
- Intravenous Anesthetics
- Muscle Relaxants
- Autonomic Drugs
- Central Nervous Drugs
- Cardiac & Diuretic Drugs
- Interactions & Genetics

PHYSICAL SCIENCES
- Applied Anatomy
- Physics and Gas Laws
- Anesthesia Machines
- Instrumentation
- Monitors and Ventilators
- Breathing Systems
- Defibrillators and Pacers

FUNDAMENTALS
- Preop. Evaluation & Prep.
- Patient Monitoring
- Airway Management
- Fluid and Blood Therapy
- Cardiopulmonary Disease
- Hepatic & Renal Disease
- Metabolic Disease
- Recovery Room

REGIONAL ANESTHESIA
- Local Anesthetics
- Autonomic Blocks
- Spinal and Epidural Blocks
- Caudal Blocks
- Upper Extremity Blocks
- Lower Extremity Blocks
- Chronic Pain Management

SPECIALTY AREAS
- Obstetric Anesthesia
- Pediatric Anesthesia
- Cardiac Anesthesia
- Thoracic Anesthesia
- Neuroanesthesia
- Ophthalmic & E.N.T.
- Geriatric and Outpatients
- Critical Care

FACULTY

Teresa Abboud, M.D.
Univ. of Southern California
Ezzat Abouleish, M.D.
U. of TX Med. Sch., Houston
Steven Barker, Ph.D., M.D.
University of California, Irvine
Jonathan Benumof, M.D.
Univ. of California, San Diego
T. A. Bowdle, M.D., Ph.D.
University of Washington
Floyd Brauer, M.D.
Loma Linda University
Burton Briggs, M.D.
Loma Linda University
Hernando DeSoto, M.D.
Riverside Hosp., Jacksonville
John Drummond, M.D.
Univ. of California, San Diego
Richard Engel, M.D.
Palomar Hosp., Escondido, CA
Christopher Gallagher, M.D.
Co-Author of *Board Stiff*
Carl Hess, M.D.
University of California, Irvine
Niels Jensen, M.D.
University of Iowa
George Khoury, M.D.
U. of California, Los Angeles
David Lubarsky, M.D.
Co-Author of *Board Stiff*
Terence Murphy, M.D.
University of Washington
Danae Powers, M.D.
Emory University
M. Nabil Rashad, M.D.
Baylor College of Medicine
Michael Ritter, M.D.
St. Louis University
Amira Safwat, M.D.
University of California, Davis
Joel Saltzman, M.D.
Las Vegas, Nevada
Mark Scheller, M.D.
Univ. of California, San Diego
Daniel Siker, M.D.
Medical College of Wisconsin
John Viljoen, M.D.
Univ. of Southern California
K.C. Wong, M.D.
University of Utah

*Accommodations were comfortable...."**

PROGRAM: This is more than a course – it is a whole program designed to prepare you for your board exams. Upon registration we will send you our home study material. At the course, one-on-one mock oral exams are held concurrent with most lectures and written question reviews. Each participant is assured a mock oral exam and observation of all non-private exams. A supplemental registration form will be sent on request to reserve mock oral sessions at any course and optional extra days of mock oral exams – April 21-23. Past participants recommend taking the course well before your exams and repeating for half price just before your exams.

*"...and those little extras...."**

LOWEST AIR FARES: Please call toll-free 1-800-548-8185 for group discounts.

*"...the most education for the money."**

FEES:

• 6 day lectures and mock orals:	$660
Residents and Fellows fee:	$440
Repeating course within 3 years:	$330
• Mock oral observation only (6 day):	$400
Per day mock oral observation:	$ 70
• Single examiner mock oral exam:	$ 70
• Dual examiner mock oral exam:	$140
• Surcharge for private exam:	$ 30
• Surcharge for videotaped exam:	$ 10
• Previous course syllabus:	$ 60

- **10% discount for fees paid more than two months before your course.**
- Attendees not in course hotel add $20/day.
- A deposit of $50 will reserve your position.
- Most home study materials will be mailed after half of the registration fee is received.

*"...home study material was extremely helpful."**

REFUNDS: Subject to $50 fee, refunds will be made up until the seminar begins.

*"I feel [the course] helped me pass ...."**

INFORMATION:

Joseph H. Selliken, Jr., M.D.
The Osler Institute
1094 Dawn Lane, P.O. Box 2218
Terre Haute, IN 47802
(800) 356-7537 or (812) 299-5658

** Comments by past Osler participants*

Limited Enrollment: ANESTHESIOLOGY REVIEW COURSE REGISTRATION

Name ____________________

Address ____________________

City/State/Zip ____________________

Phone ____________________

For: ☐ February 9-15, 1991 – Las Vegas
☐ April 15-20, 1991 – San Diego
☐ July 6-11, 1991 – Chicago
☐ Check enclosed for $______
☐ Please send more information

Mail today to:

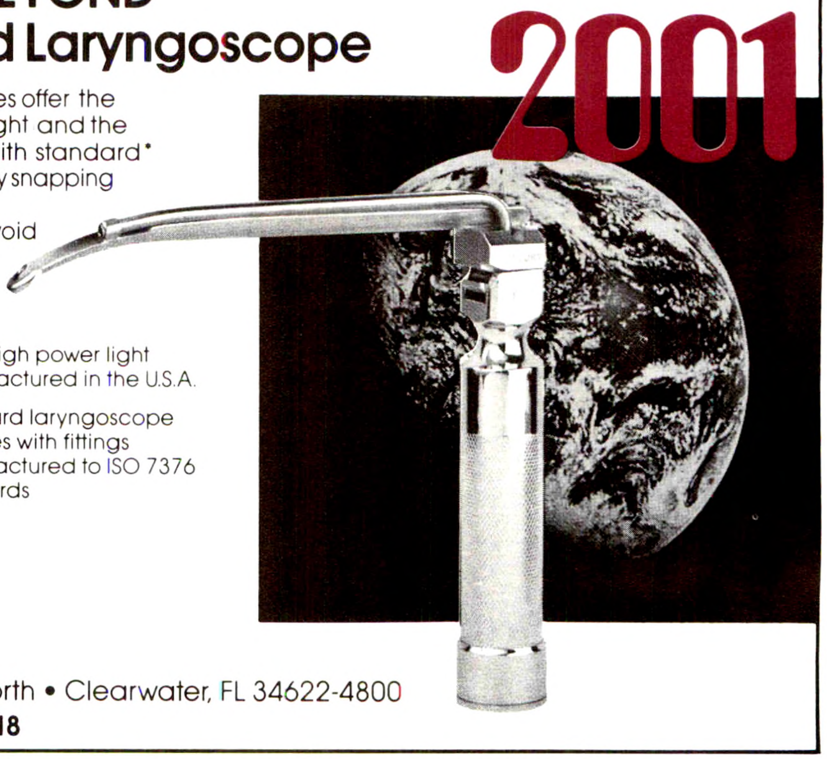
1094 Dawn Lane, Dept. B101
P.O. Box 2218
Terre Haute, IN 47802

OUR PROGRAM SIMPLY WORKS BETTER.

Malpractice insurance
exclusively for
selected anesthesiologists

PREFERRED
PHYSICIANS
MUTUAL
Risk Retention Group

Preferred Physicians Mutual
204 Lucas Place
323 West 8th Street
Kansas City, Missouri 64105
Call Toll-free 800-562-5589



MERCURY
MEDICAL

GO LIGHT YEARS BEYOND
With Your Standard Laryngoscope

The 2001 Fiberlight laryngoscope blades offer the advantages of high power halogen light and the convenience of interchangeability with standard* handles. Go light years ahead by simply snapping the Mercury 2001 Fiberlight to your standard* conventional handle, and avoid the cost of completely replacing your current laryngoscope system.

Features

- No electric wires in blade
- No electric switches
- No special handle required
- Non-glare matte finish
- Focused light
- Easy lamp replacement
- Chrome-plated brass construction
- Cool high power light
- Manufactured in the U.S.A.

*Standard laryngoscope handles with fittings manufactured to ISO 7376 standards

MERCURY
MEDICAL
11300A - 49th Street North • Clearwater, FL 34622-4800
TOLL FREE 1-800-237-6418

Anesthesiology Review Seminar

ponsored by Creighton University School of Medicine and Professional Seminars, Inc

February 10-15, 1991 Las Vegas April 15-22, 1991 San Diego

Unlimited Mock Oral Practice Sessions

hy Two Courses for One Exam
First
6 days of mock oral exams
February 10-15, 1991

Personal evaluation in comfort- e groups of **25 or less** will pinpoint as needing improvement. **Daily ictice exams** polish your thought anization and delivery techniques, s you benefit from observing as ny other sessions as you wish.

Private sessions will be avail- e and our faculty members are ;essible to answer individual ques- is throughout the course.

Home study material is avail- e upon request to enable candi- es to focus on areas needing at- tion before the course.

Then
6 days of review lectures
April 15-22, 1991

Scheduled the week before your ual board exam, this course will nbine a **thorough review** of im- tant exam topics and additional **ictice oral sessions** each day. teach the *do's* and *don'ts* of taking the oral exam and to explain how the actual exam is scored.

Attendance at these seminars **will be kept low** to enable faculty and staff to attend to the individual needs of each participant. Only the **first 100** registrations will be accepted.

For a complete list of **topics, faculty or references,** call Professional Seminars, Inc. at 1-800-445-4564 or write to P.O. Box 498, Clinton, IN 47842. To register for either course, call Creighton University, CME Division at 1-800-548-2633.

*"Your **limited registration** was definitely a plus. It gave me the opportunity to work individually with the faculty and **made me more relaxed** about the upcoming exam."*

*"Participating in the mock orals gave me the **practice and confidence I needed.** After your course, I felt prepared..."*

*"Attending your course **well in advance**...and the **review just before** my exam was the best thing I could have done to prepare for my actual exam. I passed on my **first try**."*

Creighton University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

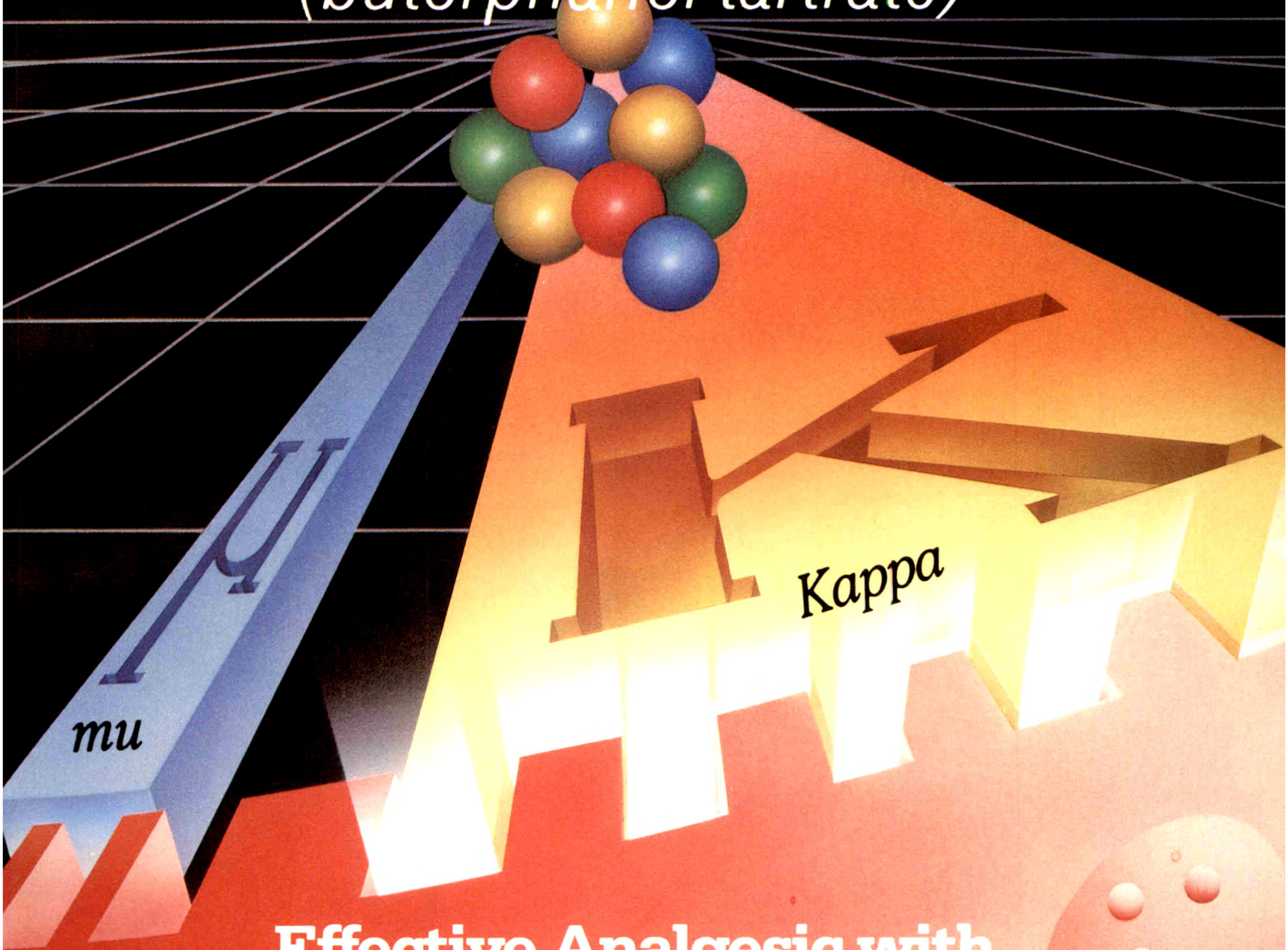
Creighton University School of Medicine designates this continuing medical education activity for **60 hours in Category 1** of the Physicians Recognition Award of the American Medical Association. One credit hour may be claimed for each hour of participation by physicians.

Name____________________
Address____________________
City/St/Zip____________________
Phone____________________
Social Security #____________________
Visa/Mastercard exp.

☐ Feb 10-15 Las Vegas ☐ April 15-20 San Diego
$600 - Las Vegas
$675 - San Diego
$1200 - Both Las Vegas & San Diego
$450 - repeating or residents
Pay to: Professional Seminars, Inc.
Mail to: Creighton University
Division of CME
California at 24th Street
Omaha, NE 68178

Stadol® IM IV

(butorphanol tartrate)



Effective Analgesic with Sedative Properties

- Premedicant for general anesthesia
- Adjunct to regional anesthesia
- For obstetrical analgesia
- Adjunct in ambulatory surgery

Anaquest

A BOC Health Care Company
Critical Care Worldwide

Artist's interpretation of Stadol molecule interacting with *kappa* and *mu* opioid receptors.

See brief summary of prescribing information on next page.

Stadol® is a Registered Trademark of Bristol-Myers Squibb Company

BRISTOL LABORATORIES
A Bristol-Myers Squibb Company
Evansville, Indiana 47721

Stadol® *(butorphanol tartrate)*

For complete information consult official package circular.

INDICATIONS AND USAGE

Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS

Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS

Patients Physically Dependent on Narcotics

Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Use During Balanced Anesthesia

Since the combined respiratory depressant effect of all intravenous medication used during conduct of general anesthesia may lead to underventilation or apnea, butorphanol should be administered during balanced anesthesia only by persons specifically trained in the use of intravenous anesthetics and adjuncts, the maintenance of a patent airway and management of respiratory effects of all intravenous medication administered.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Drug Dependence

Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure

Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects

Because Stadol increases the work of the heart, especially the pulmonary circuit, (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS

Certain Respiratory Conditions

Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function

Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery

Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Pre-operative or Pre-anesthetic Medication

Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Pregnancy

The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery

In general, the safety to the mother and fetus following the administration of Stadol during labor has been established, however, there have been a few reports of infant respiratory distress/apnea occurring after delivery (less than 1%; see Adverse Reactions). Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers

The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children

Safety and efficacy in children below age 18 years have not been established at present.

ADVERSE REACTIONS

The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations, seizures

Autonomic: flushing and warmth, dry mouth, sensitivity to cold

Cardiovascular: palpitation, increase or decrease of blood pressure

Gastrointestinal: Vomiting

Respiratory: slowing of respiration, shallow breathing, apnea

Dermatological: rash or hives

Eye: diplopia or blurred vision

OVERDOSAGE

Manifestations

Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment

The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

SUPPLY

Stadol (butorphanol tartrate Inj., USP) for I.M. or I.V. use is available as follows:
NDC 0015-5644-20 - 2 mg per mL, 2-mL vial
NDC 0015-5645-20 - 1 mg per mL, 1-mL vial
NDC 0015-5646-20 - 2 mg per mL, 1-mL vial
NDC 0015-5648-20 - 2 mg per mL, 10-mL multi-dose vial

For information on package sizes available, refer to the current price schedule.

BRISTOL LABORATORIES
Bristol-Myers
U.S. Pharmaceutical and Nutritional Group
Evansville, Indiana 47721

IARS REVIEW COURSE LECTURES AVAILABLE

____ 1990, 64th Congress—26 Review Course Lectures—$10.00

____ 1989, 63rd Congress—27 Review Course Lectures—$10.00

____ 1988, 62nd Congress—26 Review Course Lectures—$10.00

____ 1987, 61st Congress—25 Review Course Lectures—$6.00

____ 1986, 60th Congress—26 Review Course Lectures—$6.00

____ 1985, 59th Congress—26 Review Course Lectures—$6.00

____ 1984, 58th Congress—24 Review Course Lectures—$6.00

____ 1983, 57th Congress—16 Review Course Lectures—$5.00

____ 1982, 56th Congress—14 Review Course Lectures—$5.00

To:
International Anesthesia Research Society
Suite 140, 2 Summit Park Drive
Cleveland, Ohio 44131-2553

Please send Lecture Booklets checked abov

My check, payable to IARS in the amount $__________ is enclosed.

____
(Name)

____
(Mail Address)

____

____
(City, State, Zip)

12-92

ISSN 0003-2999
Volume 72, Number 1, January 1991

JCM

39

Anesthesia and Analgesia

250

157A

V.72
1-2
supp.
1991

UNIVERSITY [illegible] LIBRARY

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

The Logical Choice

P, 24,551

ANESTH ANALG 1991;72:1–4

Editorial

Halothane, Catecholamines, and Cardiac Conduction: Anything New?

Zeljko J. Bosnjak, PhD, and Lawrence A. Turner, MD

The action of anesthetics on the cardiac rhythm and their arrhythmogenic interaction with catecholamines have been subjects of interest for more than 100 yr (1). Despite the many studies over the ensuing years of the possible mechanisms underlying this adverse interaction, the cellular electrophysiologic basis for the occurrence of cardiac arrhythmias in association with endogenously released or exogenously administered catecholamines during inhalational anesthesia remains unclear. Two related studies in this issue of the journal (2,3) add to our knowledge about the electrophysiologic effects of halothane and its interaction with adrenergic agents on conduction and the refractory characteristics of ventricular tissues.

Freeman and Muir (2) first examined the effects of relatively high concentrations of halothane (0.7–1.1 mM, approximately 2–3 vol%) on conduction of action potentials in Purkinje fibers derived from the false tendons and on conduction at Purkinje fiber-muscle junctions (PF-MJ). False tendon fibers are specialized for rapid distribution of the descending cardiac impulse from the main bundle branches to the endocardium, whereas PF-MJs are specialized for the propagation of impulses from the distal Purkinje fiber layer to the three-dimensional syncytial network of endocardial muscle fibers. The authors report that halothane decreases the action potential duration (APD) of both Purkinje and ventricular muscle fibers as shown previously (4). They also observed modest depression of conduction in false tendon Purkinje fibers consistent with the reported actions of halothane reducing the rate of phase 0 depolarization (V_{max}), the action potential amplitude, and the overshoot (4). These actions of halothane on V_{max} and conduction may be reasonably attributed to depression of the peak inward Na^+ current during the upstroke of the Purkinje fiber action potential as shown in ventricular muscle fibers (5). In addition, the authors demonstrate that halothane has a pronounced depressant effect on conduction at the PF-MJ, which may be due to inhibition of active depolarization (Na^+ current) in combination with changes in passive membrane properties leading to an increase of gap junctional resistance and cell-to-cell uncoupling (6,7). The actions of agents that depress conduction at the PF-MJ may be particularly relevant to the occurrence of ventricular arrhythmias because unidirectional block is readily induced at some junctions and conduction may proceed through other junctions to propagate to the site of block in a retrograde manner, producing micro-reentry (8,9). Other mechanisms that may be responsible for the generation of arrhythmias during anesthesia are summarized elsewhere (10).

Activation of the ventricular myocardium by the Purkinje fiber network normally occurs only at specific junctional sites (9). However, an action potential from the ventricular muscle layer may propagate into the Purkinje layer at these and other sites after recovery of Purkinje fiber excitability. Moreover, there appears to be a greater margin of safety for propagation from the ventricular muscle to the Purkinje fiber layers due to greater excitability of Purkinje fibers and greater thickness of the ventricular muscle layer (11). Figure 1 is a schematic drawing of a Purkinje strand (#1) that branches into two separate bundles (#2 and #3) leading to different muscle junctions (PF-MJ 1 and PF-MJ 2) and the underlying ventricular myocardium (#4). Both junctions have a

---

Received from the Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, Wisconsin. Accepted for publication September 7, 1990.

Address correspondence to Dr. Bosnjak, Department of Anesthesiology, The Medical College of Wisconsin, MFRC-A1000, Milwaukee WI 53226.

©1991 by the International Anesthesia Research Society

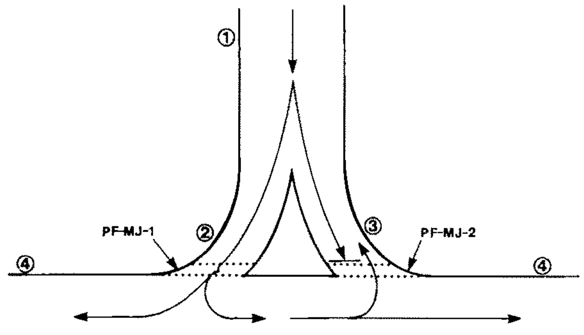


Figure 1. Unidirectional block with reentry of an impulse propagating along Purkinje strand (#1) and its branches (#2 and #3). At one Purkinje-muscle junction (PF-MJ-1) the impulse is slowed but propagates to ventricular muscle (#4). At another junction (PF-MJ-2) conduction fails, producing unidirectional block. The impulse conducted through ventricular muscle may propagate slowly in the retrograde direction through PF-MJ-2 and reexcite the Purkinje branch 3 after this segment has recovered its excitability.

low but variable safety factor for propagation from the Purkinje to muscle layers. In the presence of halothane, a reduction of cell-to-cell coupling could contribute to unidirectional block at the more susceptible junction PF-MJ 2. An increase in intercellular resistance by halothane could lead to decreased conduction velocity at either PF-MJ without major changes in active membrane properties such as changes in V_{max} (12). For segment 3 to be reentered, the action potential in the myocardium must either persist for a long time or the refractory period proximal to the site of unidirectional block must be very short. In this model, the length of the reentrant loop is a function of both the conduction velocity (θ) and refractory period of branch 3. For example, if the average conduction velocity along the pathway including the two PF-MJs and the intervening muscle is 0.1 m/s and the refractory period proximal to the site of block is 0.3 s, then the length of the reentrant circuit would be about 30 mm. This form of reentry would be facilitated by abbreviation of the refractory period proximal to the site of block (8) and by factors that slow conduction in the loop such as cell-to-cell uncoupling or local tissue injury (13). Therefore, the actions of halothane abbreviating repolarization and slowing conduction in Purkinje fibers, in combination with an action increasing PF-MJ delay, as demonstrated by Freeman and Muir (2), would be expected to facilitate the induction of reentrant activity in this model.

Ventricular arrhythmias, on the other hand, are most common during light levels of general anesthesia in association with tachycardia and hypertension secondary to sympathetic activation or administration of exogenous catecholamines. Thus, although the actions of halothane depressing conduction (Purkinje fibers and PF-MJ) and abbreviating repolarization of Purkinje and ventricular muscle fibers could be arrhythmogenic at high doses, the arrhythmias observed may be largely due to specific adrenergic receptor-mediated effects of catecholamines in combination with more modest effects of anesthetic. The second study of Freeman and Muir (3) examines the influence of α_1-adrenergic effects in combination with halothane on Purkinje fiber conduction, action potential, and refractory characteristics. The results are particularly interesting in view of an older study of Reynolds and Chiz (14) indicating that the modest slowing of Purkinje fiber conduction produced by halothane is potentiated by epinephrine and that this negative dromotropic interaction is blocked by phentolamine but not by propranolol. More recent in vivo studies have also demonstrated a synergistic relationship between α_1- and β_1-adrenoreceptor activation on the occurrence of catecholamine-induced arrhythmias during halothane anesthesia (15,16).

The electrophysiologic effects of catecholamines on Purkinje fibers are highly complex and appear to involve, but not to be limited to, opposing actions on automaticity and APD mediated by α- and β-adrenergic receptors. At low concentrations, α-adrenergic effects inhibit phase 4 diastolic depolarization, slowing automatic rate, whereas at higher concentrations β-adrenergic effects enhance phase 4 diastolic depolarization and increase the rate (17,18). In terms of repolarization characteristics, the β-effects of catecholamines decrease APD whereas α-effects increase APD (19,20). Although there are numerous studies examining the cellular and ionic mechanisms responsible for these changes, little is known about their influence on conduction of either premature or nonpremature (constant rate) impulses in the His-Purkinje system.

Freeman and Muir (3) have examined some of these complex effects on false tendon Purkinje fibers including α_1-adrenergic (methoxamine and epinephrine in the presence of β-blockade) mediated increase of APD and effective refractory period in the absence and presence of halothane. The α_1-mediated changes were opposite in direction to the abbreviation of repolarization produced by halothane alone and would appear to oppose or reduce the opportunity for a potential reentrant impulse to gain access to fully repolarized Purkinje fibers. In addition, they found that neither the α_1-mediated effects of methoxamine nor epinephrine (in the presence of propranolol) potentiated the modest slowing of conduction produced by high concentrations of halothane during constant rate pacing. These findings appear to oppose the suggestion by Reynolds and Chiz (14) that α-adrenergic receptor activation by epinephrine potentiates the negative dromotropic effects of halothane on Purkinje fibers. However, there are important differences between the two studies. Reynolds and Chiz (14) observed a decrease of conduction velocity in the presence of halothane associated with simultaneous α- and β-activation by epinephrine. In contrast, Freeman and Muir (3) investigated changes of conduction in the presence of halothane associated with the α_1-effects of a relatively pure agonist (methoxamine) and the α-effects of epinephrine, the latter only in the presence of simultaneous β-blockade with propranolol. Together, the different findings of these studies suggest that simultaneous β-adrenergic activation may be required for α-adrenergic effects to produce slowing of conduction in the presence of halothane. Finally, the authors note that the combination of an α_1-agonist (methoxamine) and halothane increases the conduction time of early premature responses. This negative dromotropic effect could contribute to increased conduction delay of rapid and irregular impulses entering the ventricular conduction system through the atrioventricular node in response to the effects of catecholamines on supraventricular pacemakers in the presence of halothane.

In some respects, these complex in vitro interactions between the effects of halothane and adrenergic agents on Purkinje fibers appear to be far removed from what might occur in vivo. However, the in vitro actions of these agents are consistent with His bundle pacing studies in which halothane was found to abbreviate refractory periods in the canine ventricular conduction system (21) and in which the effects of endogenously released norepinephrine in the presence of halothane produced nonuniform shortening of refractory periods blocked by propranolol and lengthening of refractory periods blocked by phentolamine (22). Thus, there is evidence that halothane and the α- and β-adrenergic effects of catecholamines alter conduction and refractoriness in the ventricular conduction system in vivo.

The studies by Freeman and Muir (2,3) raise a number of additional questions regarding the effects of interactions between anesthetics and catecholamines on ventricular tissues. If α-adrenergic effects in combination with halothane slow the conduction of premature responses in the major bundle branches, the possible rate dependence of this interaction is of interest because halothane-epinephrine arrhythmias typically occur at rapid heart rates (>160 beats/min) and may be overdriven at even faster rates (>220 beats/min) (23). Furthermore, if halothane substantially depresses conduction at the PF-MJ, predisposing some junctions to unidirectional block, what might be the combined effect of increasing rate and catecholamines on junctional conduction in the presence of halothane? Finally, although the effects of interactions between anesthetics and catecholamines on conduction and the refractory characteristics of Purkinje fibers are relevant to the possible induction of reentrant arrhythmias, both α- and β-adrenergic receptor activation can alter normal automaticity and the generation of triggered arrhythmias arising from after-depolarizations (24,25). It is apparent that further studies of the electrophysiologic interactions between the α- and β-adrenergic effects of catecholamines and halothane will be necessary to establish the mechanism(s) responsible for their combined adverse effects on the cardiac rhythm. Perhaps we may then come to understand the cellular basis for the occurrence of serious catecholamine-associated cardiac arrhythmias during anesthesia and surgery.

References

1. Snow J. On chloroform and other anaesthetics. London: John Churchill, 1858.
2. Freeman LC, Muir WW III. Effects of halothane on impulse propagation in Purkinje fibers and at Purkinje-muscle junctions: relationship of V_{max} to conduction velocity. Anesth Analg 1991;72:5–10.
3. Freeman LC, Muir WW III. α-Adrenoceptor stimulation in the presence of halothane: effects on impulse propagation in cardiac Purkinje fibers. Anesth Analg 1991;72:11–7.
4. Hauswirth O. Effects of halothane on single atrial, ventricular and Purkinje fibers. Circ Res 1969;24:745–50.
5. Ikemoto Y, Yatani A, Imoto Y, Arimura H. Reduction in the myocardial sodium current by halothane and thiamylal. Jpn J Physiol 1986;36:107–21.
6. Burt JM, Spray DC. Volatile anesthetics block intercellular communication between neonatal rat myocardial cells. Circ Res 1989;65:829–37.
7. Terrar DA, Victory JGG. Influence of halothane on electrical coupling in cell pairs isolated from guinea-pig ventricle. Br J Pharmacol 1988;94:509–14.
8. Sasyniuk BI, Mendez C. A mechanism for reentry in canine ventricular tissue. Circ Res 1971;28:3–15.
9. Overholt ED, Joyner RW, Veenstra RD, Rawling D, Wiedmann R. Unidirectional block between Purkinje and ventricular layers of papillary muscles. Am J Physiol 1984;247:H584–95.
10. Atlee JL III, Bosnjak ZJ. Mechanisms for cardiac dysrhythmias during anesthesia. Anesthesiology 1990;72:347–74.
11. Rawling DA, Joyner RW, Overholt ED. Variations in the functional electrical coupling between the subendocardial Purkinje and ventricular layers of the canine left ventricle. Circ Res 1985;57:252–61.
12. Jalife J, Sicouri S, Delmar M, Michaels DC. Electrical uncoupling and impulse propagation in isolated sheep Purkinje fibers. Am J Physiol 1989;257:H179–89.
13. Arnsdorf MF. Cable properties and conduction of the action potential. In: Sperelakis N, ed. Physiology and pathophysiol-

Effects of Halothane on Impulse Propagation in Purkinje Fibers and at Purkinje-Muscle Junctions: Relationship of V_{max} to Conduction Velocity

Lisa C. Freeman, DVM, PhD, and William W. Muir III, DVM, PhD

FREEMAN LC, MUIR WW III. Effects of halothane on impulse propagation in Purkinje fibers and at Purkinje-muscle junctions: relationship of V_{max} to conduction velocity. Anesth Analg 1991;72:5–10.

Alterations in Purkinje-to-muscle conduction may play a role in the development of cardiac arrhythmias. We compared the effects of halothane on impulse propagation in Purkinje fibers with its effects on impulse propagation across the Purkinje-muscle (P-M) junction. In canine Purkinje fibers, halothane (3%) significantly depressed conduction ($P < 0.05$). Exposure to halothane altered conduction velocity (θ) in a manner predicted by cable theory; a significant correlation was noted between depression of V_{max} and depression of the square of conduction velocity (θ^2) in Purkinje fibers exposed to 3% halothane ($n = 11$, $r = 0.78$, $P < 0.01$). Halothane (3%) significantly slowed impulse propagation across the P-M junction ($P < 0.05$). V_{max} and the square of apparent P-M conduction velocity were not significantly correlated ($n = 7$, $r = 0.34$, $P = 0.45$). The data demonstrate that alteration of active membrane properties can account for halothane's slowing of conduction in Purkinje fibers but not for its slowing of conduction across the P-M junction. The data also suggest that a reduction in cell-to-cell coupling may contribute to depression of Purkinje-to-muscle conduction by halothane.

Key Words: ANESTHETICS, VOLATILE—halothane. HEART, PURKINJE CONDUCTION—halothane.

The arrhythmogenic potential of volatile anesthetics, especially that of halothane, is well documented but poorly understood (1,2). Halothane is believed to aggravate arrhythmias caused by reentrant excitation (3–7). Depressed conduction is required for reentry. Halothane has been shown to moderately slow conduction in isolated Purkinje fibers and in the intact ventricle (8–14).

The negative dromotropic effect of halothane may reflect anesthetic-induced changes in either passive or active properties of cardiac tissue. Halothane has been shown to depress V_{max} and action potential amplitude by decreasing the magnitude of the fast inward sodium current (15). In addition, halothane has been shown to increase longitudinal resistance by decreasing gap junctional conductance and cell-to-cell coupling (16–20). According to one-dimensional cable theory, conduction velocity (θ) is directly related to the rate of rise of phase 0 (V_{max}) and to the amplitude of the action potential, and inversely related to the longitudinal resistance of the conduction pathway (myoplasmic + gap junctional resistance) (21,22). Drugs such as class I antiarrhythmic agents, whose negative dromotropic effects depend primarily on depression of sodium conductance, depress V_{max} and the square of conduction velocity (θ^2) in an identical fashion (22). In contrast, uncoupling agents such as alcohols and hypertonic solutions can depress conduction drastically in the absence of dramatic decreases in V_{max} (23).

To evaluate the relative importance of halothane's effects on V_{max} and intercellular coupling, we have examined the relationship between V_{max} and conduction velocity in cardiac tissue exposed to halothane. Experiments were performed to determine the effect of halothane on impulse propagation in Purkinje fibers, and across the Purkinje fiber-papillary muscle junction. Propagation across the Purkinje-muscle (P-M) junction is particularly sensitive to interventions that change not only Purkinje fiber action potential amplitude but also cell-to-cell coupling (24). Longitudinal resistance is be-

---

Supported by the Ohio State University College of Veterinary Medicine Canine Research Funds.

Received from the Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine, The Ohio State University, Columbus, Ohio. Accepted for publication June 27, 1990.

Address correspondence to Dr. Freeman, Department of Physiology, University of Rochester Medical Center, 601 Elmwood Avenue, Box 642, Rochester, NY 14642.

©1991 by the International Anesthesia Research Society

lieved to be limiting in Purkinje-to-muscle conduction but not in linear Purkinje fiber conduction pathways (25,26). On this basis, we hypothesized that (a) halothane would depress conduction across the Purkinje fiber-papillary muscle junction to a greater degree than conduction in linear Purkinje fibers; and (b) changes in V_{max} would be more closely related to changes in the square of the conduction velocity in Purkinje fibers than across the P-M junction.

Methods

Tissue Preparation

Animal use in this study was approved by the Institutional Laboratory Animal Use and Care Committee of the Ohio State University. Mongrel dogs weighing 15–25 kg were anesthetized with sodium pentobarbital (30 mg/kg IV). Their hearts were rapidly removed via right lateral thoracotomy and placed in cooled, oxygenated Tyrode's solution containing (mM): NaCl, 137; $NaHCO_3$, 12; dextrose, 5.5; NaH_2PO_4, 1.8; KCl, 4.0; $CaCl_2$, 1.8; and $MgCl_2$, 0.5. Either unbranched Purkinje fibers dissected free of ventricular muscle, or unbranched Purkinje fibers attached to a 3-cm crescent of papillary muscle of 1–2-mm thickness, were excised from the left ventricle and secured to the bottom of a tissue bath. Flow was maintained at 10 mL/min. The superfusate was aerated with a mixture of oxygen and carbon dioxide to maintain pH at 7.4 ± 0.05 and oxygen tension at 400–600 mm Hg. Temperature was maintained at 37 ± 0.5°C (model 2067 CH/P Temperature Control System, Forma Sci).

The proximal ends of Purkinje fibers were stimulated through Teflon-coated, bipolar platinum-iridium electrodes. Rectangular current pulses of 2-ms duration and two times threshold were delivered at a basic cycle length of 500 ms. Transmembrane action potentials were recorded from glass microelectrodes filled with 2.5 M KCl (DC resistance 10–30 MΩ). A Ag-AgCl junction was used to couple the microelectrodes to an amplifier with high input impedance and input capacity compensation (model M750, W-P Instruments). The recordings were displayed on the storage screens of analogue (Tektronix 5111) and digital (5110, 5D10) oscilloscopes and photographed with a Polaroid camera (C-59). Rapid chart recordings (millimeters per second) were obtained with a light-beam recording system (Honeywell 1858).

Action Potential Characteristics

Electronic differentiation was used to obtain V_{max}, the first time derivative of phase 0 of the action potential. Action potential amplitudes and durations at 50% (APD_{50}) and 90% repolarization (APD_{90}) were determined directly from chart recordings or polaroid photographs.

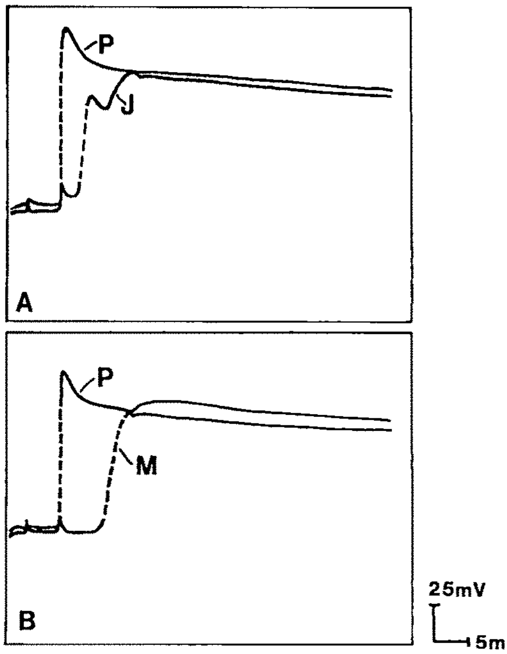


Figure 1. Junctional, Purkinje, and papillary muscle cells from the region of a P-M junction. **A.** Tracings of action potentials from Purkinje (*P*) and junctional (*J*) cells. **B.** Tracings of action potentials from the same Purkinje impalement (*P*) and from a muscle cell in the junctional region (*M*). Note correspondence between the upstroke of the muscle action potential and the second phase of the junctional action potential upstroke.

Conduction Velocity

Conduction time was defined as the time for propagation of an action potential between two intracellular microelectrodes impaled either at two sites in an unbranched free-running Purkinje fiber bundle, or at Purkinje and muscle sites in the region of the P-M junction. In Purkinje fiber preparations, impalements were localized linearly. The proximal recording electrode was placed at least 2 mm away from the stimulating electrode; proximal and distal recording electrodes were separated by distances of 4 mm or more. In P-M preparations, the P-M junction was identified by mapping the preparation with multiple (n = 20–50) microelectrode impalements and by locating the area of earliest muscle activation (24). It was possible to record junctional cell action potentials with two distinct phases of rapid depolarization (Figure 1) in the area of the P-M junction (24,27–29). As previously reported, impalements of these cells were difficult to maintain (28). Consequently, P-M conduction was measured between Purkinje and muscle cells on either side of the junctional cells. Studies of conduction were recorded at rapid oscilloscope sweep speeds (2–10 ms/division). Conduction time was measured as the interval between the midpoints of the upstrokes of the action potentials recorded at the sites described above. Interelectrode distance was measured using a stereomicroscope with calibrated eyepiece micrometer. Conduction velocity in Purkinje fibers and apparent conduction velocity at junctional sites (30) were calculated as the quotient of conduction time and interelectrode distance. Stable microelectrode impalements were maintained during control and experimental periods for all data reported here.

Drug Treatment

In preliminary experiments, the effects of 1%, 2%, and 3% halothane on conduction velocity were determined in Purkinje fibers ($n = 5$). Tissues were exposed sequentially to increasing concentrations of halothane and received 55–60-min exposure at each concentration. The effects of 3% halothane (55–60-min exposure) on action potential characteristics and conduction were then determined in additional Purkinje fiber ($n = 11$) and Purkinje fiber-papillary muscle ($n = 7$) preparations. Halothane was added to the superfusate using a calibrated vaporizer; concentrations of halothane in the superfusate were verified using gas chromatography (Varian). The reservoir of aerated Tyrode's solution was sealed, and the tissue bath was covered with an impermeable drape to minimize loss of halothane. Comparison of bath concentrations of halothane with volumetric gas standards ($n = 6$) revealed no loss of halothane in tubing between reservoir and bath, and no more than 10% loss of halothane at the bath surface. Vaporizer settings of 1%, 2%, and 3% yielded, on average, measured tissue bath concentrations of 0.33, 0.71, and 1.15 mM halothane, respectively.

Statistical Analysis

Differences in action potential characteristics and conduction times were analyzed by paired *t*-test or analysis of variance for repeated measures. Fisher's z transformation was used to compare correlations between V_{max} and θ^2 (31). A probability level of 0.05 was used to detect significant differences.

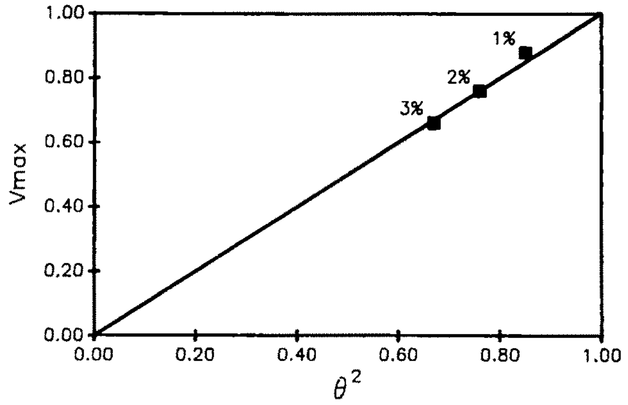


Figure 2. Concentration-dependent effects of halothane on V_{max} and conduction velocity (θ) in canine Purkinje fibers. Average data from five experiments normalized to control conditions.

Results

Halothane slowed impulse propagation in canine Purkinje fibers in a concentration-dependent fashion. Conduction velocities in Purkinje fibers ($n = 5$) exposed to increasing concentrations of halothane were as follows (m/s): control, 2.03 ± 0.07; 1%, 1.87 ± 0.08; 2%, 1.76 ± 0.08; and 3%, 1.67 ± 0.04. Conduction was significantly depressed in the presence of 3% halothane. Sequential exposure to 0%–3% halothane altered conduction velocity in a manner predicted by cable theory; that is, changes in the θ^2 were proportional to changes in V_{max} (Figure 2). Exposure of Purkinje fibers ($n = 11$) to 3% halothane also altered V_{max} and θ^2 in this predictable fashion (Figure 3A). A significant correlation was noted between depression of V_{max} and depression of θ^2 in Purkinje fibers exposed to 3% halothane ($n = 11$, $r = 0.78$, $P < 0.01$). Conduction in the presence of 3% halothane was depressed less dramatically in Purkinje fibers exposed only to 3% halothane for 1 h (Figure 3A) than in Purkinje fibers with 3-h cumulative exposure to increasing concentrations of halothane between 1% and 3% (Figure 2). We believe this difference may be attributed to accumulation of halothane in tissues with longer total anesthetic exposure. We have found only insignificant changes in conduction velocity in Purkinje fibers superfused with normal Tyrode's solution for 4–6 h.

Halothane altered the action potential characteristics of Purkinje fiber and papillary muscle cells and slowed impulse propagation across the P-M junction (Table 1). Changes in the square of apparent junctional conduction velocity were not proportional to changes in V_{max} in Purkinje fiber-papillary muscle preparations (Figure 3B). Changes in the squared rate of impulse propagation were significantly less correlated with changes in V_{max} in P-M preparations than

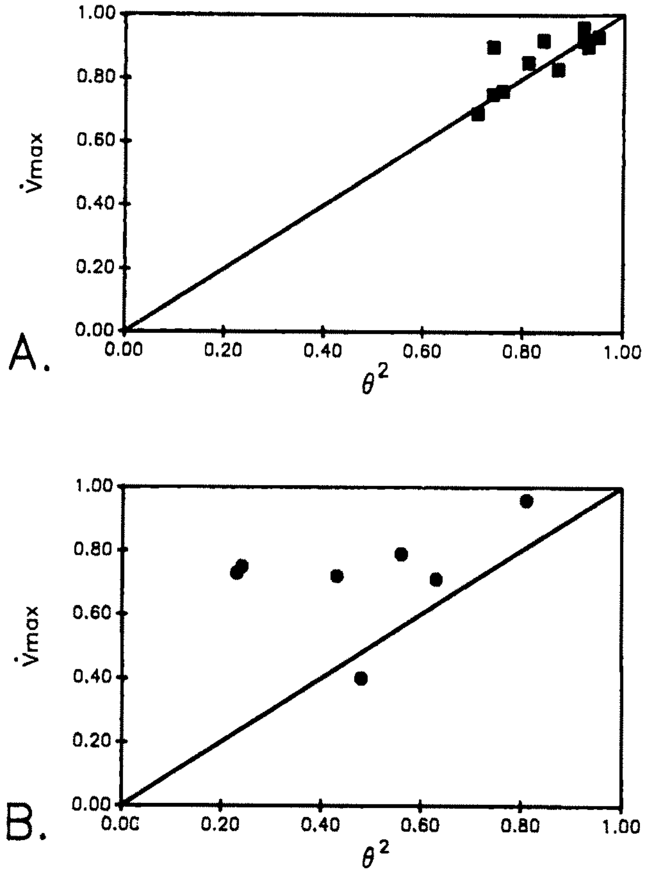


Figure 3. **A.** Effects of halothane (3%) on the relationship between V_{max} and the square of the conduction velocity (θ^2) in 11 Purkinje fibers. Data normalized to control conditions. **B.** Effects of halothane (3%) on the relationship between Purkinje fiber V_{max} and the square of apparent junctional conduction velocity (θ^2) in seven Purkinje fiber-papillary muscle preparations. Data normalized to control conditions.

in Purkinje fibers exposed to halothane; the correlation between V_{max} and the square of apparent P-M conduction velocity was statistically indistinguishable from zero ($r = 0.34$, $P = 0.45$).

Discussion

The negative dromotropic effects of halothane observed in these experiments are consistent with previous demonstrations that halothane can slow conduction in the intact ventricle and in isolated Purkinje fibers (8–14). The linear relationship between V_{max} and θ^2 in Purkinje fibers exposed to halothane suggests that in this tissue halothane's negative dromotropic effect may be related to its ability to decrease inward sodium current (15). Although it has been established that there is not a simple linear relationship between V_{max} and sodium conductance (32), it is generally accepted that, in tissues where fast inward sodium current predominates, a decrease in this current will lead to a decrease in action potential upstroke (22). Furthermore, in Purkinje fibers and papillary muscle, a number of interventions known to depress inward sodium current have been shown to decrease V_{max} in proportion to the square of conduction velocity (22,33).

Results of this study demonstrate that halothane slows impulse conduction not only in Purkinje fibers, but also at the P-M junction (Figure 3B, Table 1). The effects of halothane on impulse propagation across the P-M junction were similar in magnitude and direction to reported effects of *n*-alkanol general anesthetics such as octanol and heptanol. Octanol and heptanol have been shown to delay conduction across the P-M junction to a greater extent than conduction in Purkinje or ventricular muscle (30,34). Experimental data have revealed that octanol (0.2 mM) decreases V_{max} in proportion to the square of the conduction velocity in Purkinje fibers but not across the P-M junction (30). Heptanol (1.5–3.0 mM) has been demonstrated to slow conduction dramatically in Purkinje fibers, in proportion to changes in longitudinal resistance and in the absence of significant decreases in V_{max} (23). The effects of heptanol on conduction have been modeled successfully by computer simulations in which longitudinal resistance was increased and sodium conductance was decreased simultaneously (23). Preferential depression of P-M conduction by heptanol and octanol has been attributed not only to a decrease of Purkinje fiber upstroke velocity but also to an increase in gap junctional resistance (19,30). It is probable that halothane slows impulse propagation across the P-M junction via similar mechanisms. Halothane has been shown to increase longitudinal resistance in Purkinje fibers and ventricular muscle and to decrease electrical coupling and junctional conductance in isolated myocyte pairs (16–20). Effects of halothane on other determinants of conduction velocity, such as excitability (8) and membrane capacitance (9,35), may also contribute to its negative dromotropic effect; however, published data suggest that anesthetic effects on these parameters would be too small to account for the overall changes in impulse propagation in the absence of the well-known uncoupling effect.

In addition to conduction velocity, halothane significantly affected action potential characteristics of Purkinje fiber and ventricular muscle cells. Halothane significantly depressed Purkinje fiber action potential amplitude and V_{max} and abbreviated both Purkinje and ventricular muscle action potential durations at 50% and 90% repolarization (Table 1). These findings are consistent with previously reported effects of

Table 1. Effects of Halothane on Action Potential Characteristics and Conduction at Purkinje Fiber-Papillary Muscle Junctional Sites

Treatment	RMP (mV)	V_{max} (V/s)	APA (mV)	APD_{50} (ms)	APD_{90} (ms)	P-M dela (ms)
Purkinje fiber ($n = 7$)						
Control	−91.8 ± 2.6	545.7 ± 34.4	116.0 ± 3.3	173.6 ± 10.2	233.8 ± 10.1	
Halothane (3%)	−92.1 ± 3.6	403.7 ± 51.6[a]	109.6 ± 3.5[b]	105.6 ± 11.7[a]	184.2 ± 8.9[a]	
P-M junction ($n = 8$)						
Control						5.5 ± 1.5
Halothane (3%)						7.5 ± 1.9
Papillary muscle ($n = 7$)						
Control	−88.9 ± 2.8	NM	104.2 ± 3.2	145.2 ± 3.7	189.5 ± 5.9	
Halothane (3%)	−85.5 ± 2.9	NM	99.7 ± 2.2	127.8 ± 7.3[a]	174.8 ± 9.4[b]	

RMP, resting membrane potential; APA, action potential amplitude; APD_{50} and APD_{90}, action potental durations at 50% and 90% repolarization; P-M Purkinje-muscle; NM, not measured.

Data are presented as mean ± SEM.

[a] $P < 0.01$.

[b] $P < 0.05$.

halothane on proximal Purkinje and ventricular action potentials (6,9,14). Turner and colleagues exposed Purkinje fiber-papillary muscle preparations to 0.39 mM halothane and reported that distal Purkinje fibers were resistant to halothane abbreviation of action potential duration (6). Our use of a higher halothane concentration (1.15 mM) may account for the observed reduction of action potential duration in distal Purkinje fibers. In combination with depressed conduction, abbreviation of Purkinje fiber and papillary muscle action potential duration may enhance the potential for reentrant excitation in cardiac tissue exposed to halothane (36).

Our data analysis provides indirect evidence that the effects of halothane on both active and passive membrane properties can influence intracardiac conduction. Yet the limiting assumptions inherent in one-dimensional cable analysis must be considered. Although the relationship between V_{max} and conduction velocity (θ) predicted by the cable equation has been demonstrated experimentally in Purkinje fibers and papillary muscle (22,33), neither Purkinje fibers nor papillary muscles actually behave as continuous cables (37). The P-M junction has been described as a complex three-dimensional system (28,38) and almost certainly does not meet the requirements of a continuous cable. One-dimensional cable theory has not been previously applied to conduction across the P-M junction. It is unlikely, however, that the poor correlation between changes in V_{max} and changes in the square of the apparent conduction velocity in P-M junction preparations exposed to halothane reflects only difficulty in applying the one-dimensional cable model to the P-M junction. Application of the cable model to data reported by Veenstra and colleagues (38) confirms that the model is appropriate to P-M conduction; in thei study of quinidine effects on impulse propagation, V_{ma} decreased in proportion to the square of conductio velocity not only in linear papillary muscle but als across the P-M junction (data presented in Figure 11 o Reference 38).

The purpose of the present experiments was t compare the effects of halothane on impulse propagation in Purkinje fibers with the effects of halothan on impulse propagation across the P-M junction. Th negative dromotropic effect of halothane was mor pronounced at the P-M junction than in linear Purkinje fibers (Figure 3). Whereas halothane depressio of conduction in Purkinje fibers could be accounte for by reduction in action potential amplitude an upstroke velocity, the effect of halothane on P-M conduction appeared to involve changes in bot active and passive membrane properties in the junctional region. We demonstrated halothane-mediate reduction in Purkinje fiber action potential amplitud and V_{max} that would decrease the input to the junction. Others have established that halothane increases longitudinal (gap junctional) resistance i Purkinje fibers and ventricular muscle (16–20); it i likely that halothane's depressant effects on cell-to cell coupling play a prominent role in decreasin conduction across the P-M junction, a region o intrinsically poor cell coupling (25,39). The P-M junction has been identified as a potential site for th initiation and termination of cardiac arrhythmia (24,34,36,39); thus, the observed depression of P-M conduction by halothane is consistent with the hypothesis that reduction of intracellular coupling during halothane exposure contributes to the occurrenc of arrhythmias. Generalization of these data, ob tained in isolated tissue, to clinical situations involving anesthetized animals or humans must be done with caution.

We thank Dr. Robert F. Gilmour, Jr. and his associate Michelle Buddle for helping us to establish the P-M preparation in our laboratory. Technical assistance from Jan Sally and Linda Bednarski is also appreciated.

References

1. Johnson RR, Eger EI, Wilson C. A comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man. Anesth Analg 1976;55:709–12.
2. Reynolds AK. On the mechanism of myocardial sensitization to catecholamines by hydrocarbon anesthetics. Can J Physiol Pharmacol 1984;62:183–98.
3. Hashimoto K, Endoh E, Kimura T, Hashimoto K. Effects of halothane on automaticity and contractile force of isolated, blood perfused canine ventricular tissue. Anesthesiology 1975;42:15–25.
4. Kapur PA, Flacke WE. Epinephrine-induced arrhythmias and cardiovascular function after verapamil during halothane anesthesia in the dog. Anesthesiology 1981;55:218–25.
5. Atlee JL. Halothane: cause or cure for arrhythmias. Anesthesiology 1987;67:617–8.
6. Turner LA, Bosnjak ZJ, Kampine JP. Actions of halothane on the electrical activity of the Purkinje fibers derived from normal and infarcted canine hearts. Anesthesiology 1987;67:619–29.
7. Hayashi Y, Sumikawa K, Tashiro C, Yoshiya I. Synergistic interaction of α_1- and β-adrenoreceptor agonists on induction arrhythmias during halothane anesthesia in dogs. Anesthesiology 1988;68:902–7.
8. Smith SL, Webb WR, Fabian LW, Hagaman VD. Cardiac excitability in ether cyclopropane and halothane anesthesia. Anesthesiology 1962;23:766–75.
9. Hauswirth O. Effects of halothane on single atrial, ventricular, and Purkinje fibers. Circ Res 1969;24:745–50.
10. Atlee JL, Homer LD, Tobey RE. Diphenylhydantoin and lidocaine modification of A-V conduction in halothane-anesthetized dogs. Anesthesiology 1975;43:49–60.
11. Atlee JL, Alexander SC. Halothane effects on conductivity of the AV node and His-Purkinje system in the dog. Anesth Analg 1977;56:378–86.
12. Reynolds AK, Chiz JF. Epinephrine-potentiated slowing of conduction in Purkinje fibers. Res Commun Chem Pathol Pharmacol 1974;9:633–45.
13. Stowe DF, Bosnjak ZJ, Marijic J, Kampine JP. Effects of halothane with and without histamine and/or epinephrine on automaticity, intracardiac conduction times, and development of dysrhythmias in the isolated guinea pig heart. Anesthesiology 1988;68:695–706.
14. Freeman LC, Muir WW III. α-Adrenoceptor stimulation in the presence of halothane: effects on impulse propagation in cardiac Purkinje fibers. Anesth Analg 1991;72:11–7.
15. Ikemoto Y, Yatani A, Imoto Y, Arimura H. Reduction in the myocardial sodium current by halothane and thiamylal. Jpn J Physiol 1986;36:107–21.
16. Hauswirth O. The influence of halothane on electrical properties of cardiac Purkinje fibers. J Physiol 1968;201:42P–3P.
17. Wojtczak JA. Electrical uncoupling induced by general anesthetics: a calcium-independent process? In: Bennet MVL, Spray DC, eds. Gap junctions. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1985:167–75.
18. Terrar DA, Victory JGG. Influence of halothane on electrical coupling in cell pairs isolated from guinea-pig ventricle. Br J Pharmacol 1988;94:509–14.
19. Niggli E, Rudisuli A, Maurer P, Weingart R. Effects of general anesthetics on current flow across membranes in guinea pig myocytes. Am J Physiol 1989;256:C273–81.
20. Burt JM, Spray DC. Volatile anesthetics block intercellular communication between neonatal rat myocardial cells. Circ Res 1989;65:829–37.
21. Hunter PJ, McHaughton PA, Noble D. Analytical models of propagation in excitable cells. Prog Biophys Mol Biol 1975;30:99–144.
22. Buchanan JW, Saito T, Gettes I. The effects of antiarrhythmic drugs, stimulation frequency, and potassium induced resting potential changes on conduction velocity and dV/dt in guinea pig myocardium. Circ Res 1985;56:696–703.
23. Jalife J, Sicouri S, Delmar M, Michaels DC. Electrical uncoupling and impulse propagation in isolated sheep Purkinje fibers. Am J Physiol 1989;257:H179–89.
24. Gilmour RF, Evans JJ, Zipes DP. Preferential interruptions of impulse transmission across Purkinje-muscle junctions by interventions that depress conduction. In: Zipes DP, Jalife JJ, eds. Cardiac electrophysiology and arrhythmias. Orlando, Fla.: Grune & Stratton, 1985:287–300.
25. Joyner RW. Effects of the discrete pattern of electrical coupling on propagation through an electrical syncytium. Circ Res 1982;50:192–200.
26. Burt J, Spray DC. Inotropic agents modulate gap junctional conductance between cardiac myocytes. Am J Physiol 1988; 254:H1206–10.
27. Alanis J, Benitez D. Rate of rise of Purkinje and transitional cells action potential and the propagation across the Purkinje-myocardium junction. Jpn J Physiol 1970;20:217–32.
28. Mendez C, Mueller WJ, Urguiaga X. Propagation of impulses across the Purkinje fiber-muscle junctions in the dog heart. Circ Res 1970;26:135–50.
29. Rawling DA, Joyner RW. Characteristics of junctional regions between Purkinje and ventricular muscle cells of canine ventricular subendocardium. Circ Res 1987;60:580–5.
30. Joyner R, Overholt ED. Effects of octanol on subendocardial Purkinje-to-ventricular transmission. Am J Physiol 1985;249: H1228–31.
31. Snedecor GW, Cochran WG. Statistical methods. 7th ed. Ames, Iowa: The Iowa State University Press, 1980:186.
32. Strichartz G, Cohen I. V_{max} as a measure of gNa in nerve and cardiac membranes. Biophys J 1978;23:153–6.
33. Walton MK, Fozzard HA. The conducted action potential: models and comparison to experiments. Biophys J 1983;44:9–26.
34. Gilmour RF. Phase-resetting of circus movement reentry in cardiac tissue. In: Zipes DP, Jalife J, eds. Cardiac electrophysiology from cell to bedside. Philadelphia: WB Saunders, 1990: 396–402.
35. Franks NP, Lieb WR. Molecular mechanisms of general anesthesia. Nature 1982;300:487–93.
36. Sasyniuk BI, Mendez C. A mechanism for reentry in canine ventricular tissue. Circ Res 1971;28:3–15.
37. Rudy Y, Quan WL. A model of the effects of the discrete cellular structure on electrical propagation in cardiac tissues. Circ Res 1987;61:815–23.
38. Veenstra RD, Joyner RW, Rawling DA. Purkinje and ventricular activation sequences of canine papillary muscle. Effects of quinidine and calcium on the Purkinje-ventricular conduction delay. Circ Res 1984;54:500–15.
39. Rawling DA, Joyner RW, Overholt ED. Variations in the functional electrical coupling between the subendocardial Purkinje and ventricular layers the canine left ventricle. Circ Res 1985;57:252–61.

α-Adrenoceptor Stimulation in the Presence of Halothane: Effects on Impulse Propagation in Cardiac Purkinje Fibers

Lisa C. Freeman, DVM, PhD, and William W. Muir III, DVM, PhD

FREEMAN LC, MUIR WW III. α-Adrenoceptor stimulation in the presence of halothane: effects on impulse propagation in cardiac Purkinje fibers. Anesth Analg 1991;72:11–7.

Halothane effects on action potential characteristics and conduction were determined in canine Purkinje fibers, before and during α-adrenergic stimulation. Halothane significantly decreased effective refractory period and action potential duration in Purkinje fibers. α-Adrenergic stimulation restored effective refractory period and action potential duration in Purkinje fibers exposed to halothane via an α_1-adrenoceptor mediated effect antagonized by prazosin. Halothane significantly slowed propagation of impulses initiated at a basic cycle length of 500 ms, and conduction of premature impulses, in Purkinje fibers. In the presence of halothane, α-adrenergic stimulation had no additional effects on normal impulse propagation; however, α-adrenergic stimulation significantly slowed the conduction of premature impulses in Purkinje fibers exposed to halothane. These data refute a previous report that α-adrenergic stimulation enhances halothane's negative dromotropic effect in Purkinje fibers paced at a basic drive cycle length. α-Adrenergic prolongation of the conduction times of premature stimuli in Purkinje fibers exposed to halothane is a new finding.

Key Words: ANESTHETICS, VOLATILE—halothane. HEART, PURKINJE IMPULSE PROPAGATION—halothane.

Volatile anesthetics can reduce the dose of exogenously administered catecholamines required to produce a cardiac arrhythmia (1). Of the modern anesthetics, halothane is most notorious for its ability to sensitize the myocardium to the arrhythmogenic effects of adrenergic amines (1,2); concurrent administration of epinephrine during halothane anesthesia can trigger life-threatening ventricular arrhythmias (3). Despite extensive investigation, the phenomenon of myocardial sensitization is poorly understood. The relative contributions of β- and α_1-adrenergic stimulation to the arrhythmogenicity of epinephrine during halothane anesthesia have been the focus of several investigations, and evidence suggests that both β- and α_1-adrenoceptors mediate induction of ventricular arrhythmias (4–8). Halothane has been shown to decrease the refractory period of Purkinje fibers and to slow conduction in the atrioventricular node, ventricle, and isolated Purkinje fibers (9–13) Epinephrine was reported to potentiate the negative dromotropic effect of halothane in Purkinje fibers and this synergistic interaction was prevented by the α-adrenergic antagonist phentolamine (11). Together these findings provide a basis for the assumption that a reentrant mechanism underlies the arrhythmogenic interaction between halothane and α-adrenergic agonists (1,8,11).

α-Adrenergic enhancement of halothane's negative dromotropic effect has not previously been investigated using specific α_1-adrenergic agonists or antagonists. In the present study, the effects of halothane on action potential characteristics and conduction were determined in canine Purkinje fibers, before and during α-adrenergic stimulation with not only the mixed α- and β-adrenergic agonist epinephrine but also the specific α_1-adrenergic agonist methoxamine.

Methods

Tissue Preparation

Animal use in these experiments was approved by the Institutional Laboratory Animal Use and Care

---

Supported by the Ohio State University College of Veterinary Medicine Canine Research Funds.

Received from the Departments of Veterinary Physiology and Pharmacology, College of Veterinary Medicine, The Ohio State University, Columbus, Ohio. Accepted for publication August 6, 1990.

Address correspondence to Dr. Freeman, Department of Physiology, University of Rochester Medical Center, 601 Elmwood Avenue, Box 642, Rochester, NY 14642.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Committee of the Ohio State University. Mongrel dogs weighing 15–25 kg were anesthetized with sodium pentobarbital (30 mg/kg IV). Their hearts were rapidly removed via right lateral thoracotomy and placed in cooled, oxygenated Tyrode's solution containing (mM): NaCl, 137; $NaHCO_3$, 12; dextrose, 5.5; NaH_2PO_4, 1.8; KCl, 4.0; $CaCl_2$, 1.8; and $MgCl_2$, 0.5. False tendons dissected free of ventricular muscle were excised from either ventricle and were secured to the bottom of a Lucite perfusion chamber. Flow was maintained at 15 mL/min, and the depth of perfusate above the tissue was maintained at or above 1 mm. The superfusate was aerated with a mixture of oxygen and carbon dioxide to maintain pH at 7.4 ± 0.05 and oxygen tension at 400–600 mm Hg. Temperature was maintained at 37 ± 0.5°C (model 2067 CH/P Temperature Control System, Forma Sci). One Purkinje fiber from each heart was used for the collection of data.

The proximal ends of Purkinje fibers were stimulated externally through bipolar electrodes. Rectangular current pulses of 2-ms duration and two times threshold were delivered at a basic cycle length (BCL) of 500 or 1000 ms. Transmembrane action potentials were recorded from glass microelectrodes filled with 2.5 M KCl (DC resistance, 10–30 MΩ). A Ag-AgCl junction was used to couple the microelectrodes to an amplifier with high input impedance and input capacity compensation (model M750, W-P Instruments). The recordings were displayed on the storage screens of analogue (Tektronix 5111) and digital (5110, 5D10) oscilloscopes and photographed with a Polaroid camera (C-59). Rapid chart recordings (millimeters per second) were obtained with a light-beam recording system (Honeywell 1858).

Action Potential Characteristics

Action potential amplitude and action potential duration at 50% (APD_{50}), 75% (APD_{75}), and 90% repolarization (APD_{90}) were determined directly from chart recordings or polaroid photographs. The slopes of action potential phases 2 (SP2) and 3 (SP3) were determined using the cursors and digital readout of the digital oscilloscope. Effective refractory period (ERP), defined as the period after an action potential upstroke during which a subsequent premature action potential could not be stimulated, was determined using delivery of a premature stimulus after a train of 10 action potentials at the basic drive cycle length. Drug effects on conduction of premature impulses were evaluated using a similar extrastimulus technique, where trains of 10 drive stimuli were followed by a premature stimulus of variable coupling interval and a subsequent pause of 2 s for observation of induced responses.

Conduction Time

Conduction time was defined as the time for propagation of an action potential between two intracellular microelectrodes impaled in an unbranched Purkinje fiber bundle; impalements were localized linearly. The proximal recording electrode was placed at least 2 mm away from the stimulating electrode. Proximal and distal impalements were separated by at least 4 mm. Studies of conduction were recorded at rapid oscilloscope sweep speeds (2–10 ms/division). Conduction time was measured as the interval between the midpoints of the upstrokes of the action potentials recorded at the sites described above. Interelectrode distance was measured with a calibrated eyepiece micrometer. Conduction velocity was calculated as the quotient of conduction time and interelectrode distance.

Drug Protocols

Electrophysiologic effects of 1%, 2%, and 3% halothane (Halocarbon Laboratories) were determined in canine Purkinje fibers sequentially exposed to increasing concentrations of halothane. Halothane in oxygen was introduced to the perfusate reservoir from a calibrated vaporizer. Concentrations of halothane in the tissue bath were measured using gas chromatography (Varian); vaporizer settings of 1%, 2%, and 3% yielded average halothane concentrations of 0.33, 0.71, and 1.15 mM halothane after 45–50 min of superfusion with preequilibrated solution.

Electrophysiologic effects of methoxamine (Burroughs Wellcome) were determined in canine Purkinje fibers. A concentration-response curve was generated for 10^{-9}–10^{-5} M methoxamine; superfusion at each concentration of methoxamine lasted 20–25 min.

The effects of 3% halothane on Purkinje fibers were determined during superfusion first with normal Tyrode's solution, then with Tyrode's solution containing either 5×10^{-6} M methoxamine or 10^{-6} M (−)epinephrine (Sigma) in the presence of 5×10^{-7} M (−)propranolol (Sigma). In solutions containing methoxamine or epinephrine, ascorbate (0.3%, wt/vol) was added as an antioxidant. At this concentration, ascorbate alone had no effect on the parameters measured.

The specific α_1-adrenoceptor antagonist prazosin (Sigma) was used at a concentration of 5×10^{-7} M in

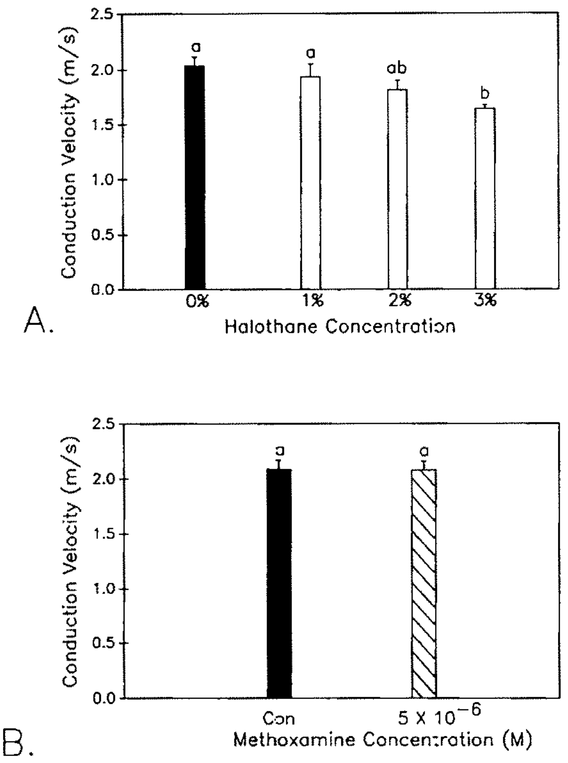


Figure 1. Individual effects of halothane and α-adrenoceptor stimulation on impulse conduction in cardiac Purkinje fibers. Bars without common superscripts are significantly different at $P < 0.05$. Con, control (*solid bar*). **A.** Concentration-dependent negative dromotropic effect of halothane in Purkinje fibers (BCL = 500, $n = 4$). **B.** Methoxamine (*striped bar*) did not affect conduction in Purkinje fibers at concentrations in the range 10^{-9}–10^{-5} M. Lack of effect at 5×10^{-6} M shown here (BCL = 500, $n = 3$).

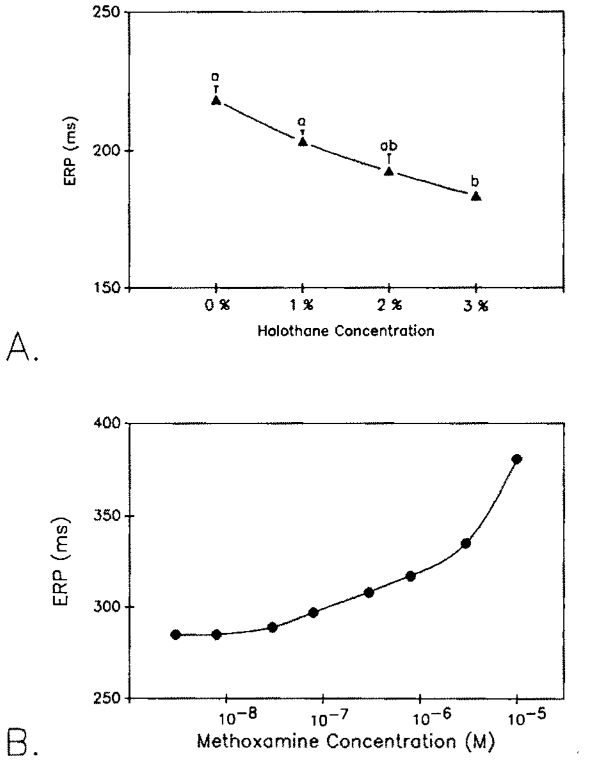


Figure 2. Individual effects of halothane and α-adrenoceptor stim ulation on ERP in Purkinje fibers. **A.** Concentration-dependen effects of halothane on ERP in Purkinje fibers. Points withou common superscripts are significantly different at $P < 0.05$ (BCL = 500, $n = 6$). **B.** Concentration-dependent effects of methoxamin on ERP in Purkinje fibers. A representative experiment (BCL = 1000).

selected experiments to block the effects of methoxamine or epinephrine. Prazosin was dissolved in a small volume of dimethylsulfoxide and serially diluted in aqueous solution. At its maximal concentration in bath solutions, 0.002% (vol/vol), dimethylsulfoxide had no effect on the parameters measured.

Data Analysis

Univariate and multivariate analysis of variance for repeated measures were used to detect significant differences within and between groups. Multiple comparisons were made using Duncan's multiple-range test or the Bonferroni inequality. A probability level less than 0.05 was considered to be significant.

Results

The individual effects of halothane and α-adrenergic stimulation on determinants of reentry are shown in Figures 1 and 2. Halothane significantly decrease conduction velocity (Figure 1) and ERP (Figure 2) i Purkinje fibers, in a concentration-dependent fash ion. Halothane abbreviation of refractoriness wa associated with concentration-dependent decrease in action potential duration (data not shown). Meth oxamine had no effect on conduction velocity (Figur 1) and increased ERP in Purkinje fibers in a concen tration-dependent fashion ($n = 4$, $P < 0.05$, Figure 2) Methoxamine prolongation of refractoriness was as sociated with increased action potential duratio (data not shown).

In Purkinje fibers, halothane (3.0%) significantl slowed not only propagation of impulses initiated a the basic cycle length (Figure 3) but also conductio of premature impulses ($n = 7$, $P < 0.05$, Figure 4). I three Purkinje fiber preparations that were exclude from data analysis, halothane altered the conductio pathway of premature impulses. In the presence o halothane, methoxamine had no additional effect o normal impulse propagation in Purkinje fibers (Fig ure 3); however, methoxamine significantly slowe the conduction of premature impulses in Purkinj

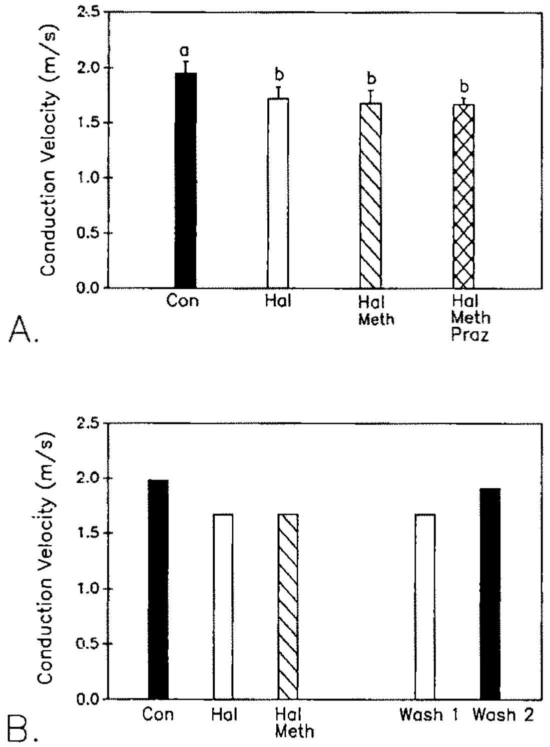


Figure 3. Combined effects of halothane and α-adrenergic stimulation on impulse propagation in Purkinje fibers. **A.** Effect of 5×10^{-6} M methoxamine (Meth, *striped bar*) on conduction velocity in Purkinje fibers exposed to 3% halothane (Hal, *clear bar*), in the absence and presence of 5×10^{-7} M prazosin (Praz, *cross-hatched bar*). Bars without common superscripts are significantly different at $P < 0.05$. Con, control (*solid bar*), (BCL = 500, $n = 6$). **B.** Representative experiment showing sequential washout of first Meth (Wash 1) and then Hal (Wash 2). During Wash 1, Purkinje fibers were reexposed to 3% halothane alone. Wash 2 represented a return to control conditions.

fibers exposed to halothane ($n = 7$, $P < 0.05$, Figure 4). Halothane significantly decreased ERP and action potential duration in Purkinje fibers; halothane-induced decreases in APD_{50}, APD_{75}, and APD_{90} were associated with increased SP2 and decreased SP3 of the action potential (Table 1). Methoxamine restored ERP and APD_{90} in Purkinje fibers exposed to halothane by further decreasing SP3 via an α_1-adrenergic mechanism (Table 1, Figure 5). In the presence of halothane, α-adrenergic effects of epinephrine on action potential characteristics and conduction were similar to those of methoxamine (Table 2, Figure 6).

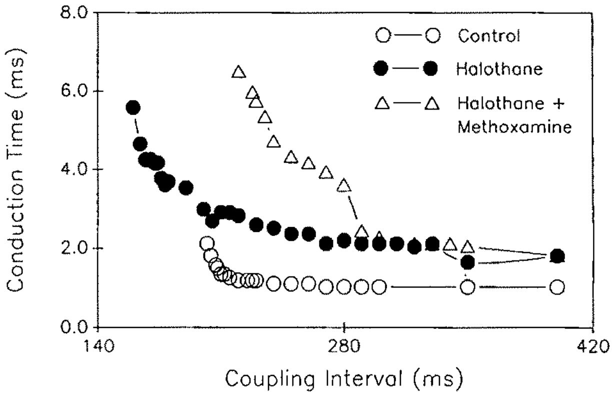


Figure 4. Effects of methoxamine in the presence of halothane on the conduction of premature impulses in Purkinje fibers. A representative experiment ($n = 7$). Halothane (3%) decreased ERP and slowed the conduction of premature impulses. The addition of methoxamine (5×10^{-6} M) restored ERP while further delaying conduction of premature impulses.

Discussion

This is the first report of the combined effects of halothane and α-adrenergic stimulation on action potential characteristics and conduction of premature impulses in Purkinje fibers. Furthermore, the present study differs from previous investigations by using a specific agonist and antagonist to evaluate α-adrenergic effects in the presence of halothane.

Halothane had profound effects on action potential characteristics in Purkinje fibers (Tables 1 and 2). Halothane has been shown previously to decrease action potential amplitude, overshoot, and upstroke velocity (V_{max}) of Purkinje fiber and ventricular action potentials (9,14–16); these effects have been associated with depression of sodium conductance (14). Halothane's ability to accelerate repolarization during the plateau phase of the ventricular action potential and its ability to shorten action potential duration have been reported and attributed to a depressant effect on the slow inward calcium current (17,18). In addition, an effect of halothane on sodium window current may play a role in abbreviation of the Purkinje fiber action potential plateau (15). The halothane-induced decrease in the rate of repolarization during phase 3 of the action potential may reflect depression of outward repolarizing currents, including I_{k1} and I_x (16,19). Halothane's depressant effects on outward currents have little effect on action potential duration because its greater inhibitory effects on opposing inward currents predominate (19).

α-Adrenergic stimulation increased ERP, APD_{90}, and SP3 of Purkinje fiber action potentials, both in the presence and absence of halothane (Tables 1 and 2). Adrenergic amines have been shown to prolong refractoriness and action potential duration by lengthening the plateau and slowing phase 3 repolarization (20–24), and these effects have been attributed to stimulation of α_1-adrenoceptors (23,24). The identity of the ionic currents responsible for α_1-adrenergic

Table 1. Effects on Action Potential Characteristics of α-Adrenergic Stimulation With Methoxamine, in the Presence and Absence of Halothane

Treatment	ERP (ms)	APA (mV)	APD_{50} (ms)	APD_{75} (ms)	APD_{90} (ms)	Slope 2 (mV/s)	Slope 3 (mV/s)
Control (*n* = 18)	210.4 ± 3.9^a	122.8 ± 1.2^a	167.7 ± 5.3^a	219.4 ± 6.8^a	250.6 ± 5.7^a	-109.0 ± 10^a	-459.7 ± 32^a
Halothane (3%) (*n* = 17)	179.4 ± 1.3^b	114.5 ± 2.2^b	107.6 ± 6.2^b	$173.5 \pm 5.4^{b,c}$	220.9 ± 3.8^b	-198.8 ± 21^b	-247.3 ± 10^b
Hal/Meth (*n* = 14)	214.4 ± 6.9^a	116.1 ± 2.2^b	116.1 ± 4.9^b	188.6 ± 3.8^b	248.6 ± 4.5^a	-205.3 ± 22^b	-215.7 ± 10^c
Hal/Meth/Praz (*n* = 6)	189.4 ± 6.4^b	111.8 ± 4.5^b	102.4 ± 8.9^b	169.9 ± 8.0^c	214.7 ± 3.9^b	-245.0 ± 13^c	$-240.8 \pm 38^{b,c}$

ERP, effective refractory period; APA, action potential amplitude; APD_{50}, APD_{75}, APD_{90}, action potential durations at 50%, 75%, and 90% repolarization, respectively; Hal, halothane (3%); Meth, methoxamine (5×10^{-6} M); Praz, prazosin (5×10^{-7} M).

Data presented as mean ± SEM.

Within a single column, means without common superscripts differ significantly at $P < 0.05$.

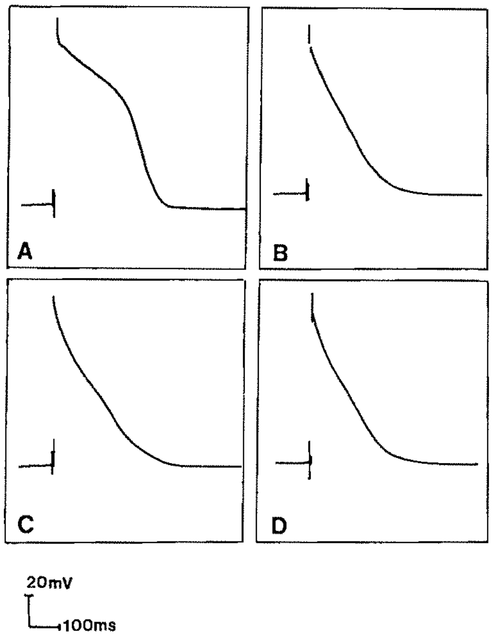


Figure 5. Combined effects of halothane and methoxamine on Purkinje fiber action potentials (BCL = 500). **A**, Control; **B**, halothane (3%); **C**, halothane + methoxamine (5×10^{-6} M); **D**, halothane, methoxamine, + prazosin (5×10^{-7} M).

effects on the action potential is controversial. It has been suggested that α-adrenoceptor stimulation increased action potential duration by increasing inward calcium current (25,26); however, recent studies of isolated myocytes have failed to demonstrate any stimulatory effect (24,27). Prolongation of action potential duration by α_1-adrenoceptor stimulation may be mediated by inhibition of outward repolarizing potassium current (24,28–30). Regardless of the specific ionic mechanisms involved, α-adrenergic stimulation in the presence of halothane restores the overall balance between inward and outward currents that is altered by the anesthetic, as evidenced by restoration of ERP and APD_{90}. In Purkinje fibers exposed to halothane in combination with either methoxamine, or epinephrine plus propranolol, prazosin restored ERP and action potential duration to values seen during exposure to halothane alone (Tables 1 and 2). Any effect of prazosin itself on ERP or action potential duration would have been opposite in direction (31,32); thus, the observed effects of methoxamine and epinephrine on action potential characteristics were mediated by α_1-adrenoceptors. A slight depressant effect of the α_1-antagonist prazosin on action potential amplitude was noted in these experiments (Tables 1 and 2); similar effects of prazosin on action potential amplitude have been reported previously at 2- to 10-fold higher than the present concentrations of the antagonist (23,31,32).

These data (Figure 3) refute a previous report that α-adrenergic stimulation enhances halothane's negative dromotropic effect in Purkinje fibers. Reynolds and Chiz reported that, at concentrations with no significant effect on conduction velocity in canine Purkinje fibers, epinephrine markedly potentiated a modest slowing of conduction produced by halothane; this effect was antagonized by an α-, but not a β-, adrenergic antagonist (11). The experimental preparations and drug concentrations employed in the studies of Reynolds and Chiz were similar to those used in the current study. The reasons for the differences between their findings and ours are not clear. In the absence of halothane, α_1-adrenergic stimulation has not been shown to have profound effects on conduction velocity (Figure 1) (11), or the determinants of conduction velocity such as V_{max} (22,23), action potential amplitude (20,21), and gap junctional resistance (33). Halothane did not change the magnitude or direction of the α-adrenoceptor mediated effect on ERP (Tables 1 and 2). Halothane has been shown to have no effects on α_1-adrenoceptor mediated responses in other tissues (34,35).

α-Adrenergic prolongation of the conduction times of premature stimuli in Purkinje fibers exposed to halothane is a new finding. Depressed conduction of premature impulses initiated at short coupling intervals in the presence of methoxamine is probably

Table 2. Effects on Action Potential Characteristics and Conduction Velocity of α-Adrenergic Stimulation With Epinephrine, in the Presence and Absence of Halothane

Treatment	CV (m/s) (n = 6)	ERP (ms) (n = 11)	APA (mV) (n = 11)	APD_{50} (ms) (n = 11)	APD_{75} (ms) (n = 11)	APD_{90} (ms) (n = 11)
Control	2.5 ± 0.3^a	198.5 ± 6.7^a	121.3 ± 1.0^a	165.2 ± 7.8^a	198.6 ± 7.7^a	227.8 ± 7.2^a
Propranolol	2.5 ± 0.3^a	196.8 ± 6.3^a	121.1 ± 1.1^a	160.5 ± 5.5^a	198.7 ± 7.4^a	228.8 ± 7.0^a
Propranolol/Hal	2.2 ± 0.3^b	167.4 ± 3.8^b	115.7 ± 1.5^b	93.8 ± $3.4^{b,c}$	151.3 ± 3.0^b	194.7 ± 3.7^b
Propranolol/Hal/Epi	2.1 ± 0.3^b	191.8 ± 4.8^a	117.6 ± 1.3^b	106.2 ± 2.7^b	175.2 ± 2.7^c	220.8 ± 4.8^a
Propranolol/Hal/Epi/Praz	2.1 ± 0.4^b	170.9 ± 4.4^b	112.9 ± 2.2^c	85.9 ± 2.6^c	146.7 ± 3.2^b	196.1 ± 5.9^b

Epi, epinephrine (1 × 10^{-6} M). All other abbreviations as in Table 1.
Data presented are mean ± SEM.
Within a single column, means without common superscripts differ significantly at $P < 0.05$.

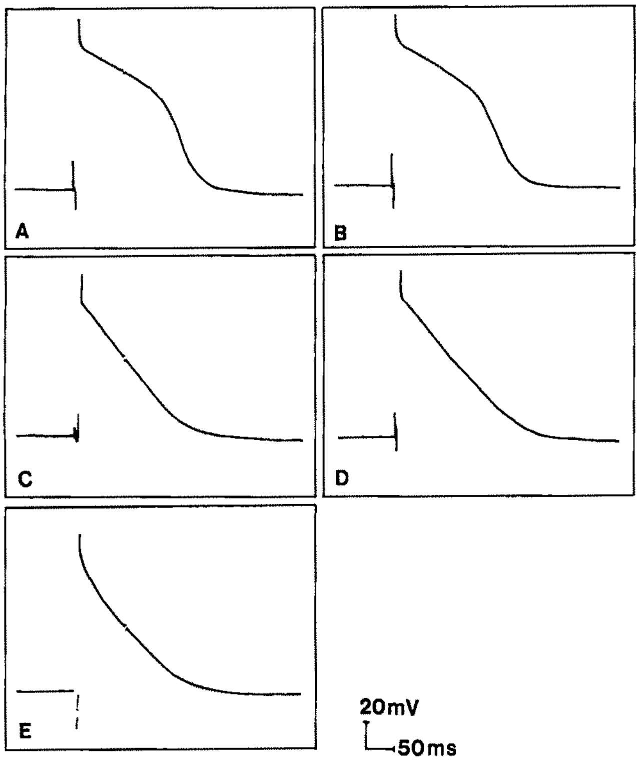


Figure 6. Combined effects of halothane and epinephrine, in the presence of propranolol, on Purkinje fiber action potentials (BCL = 500). **A**, Control; **B**, propranolol (5 × 10^{-7} M); **C**, propranolol + halothane (3%); **D**, propranolol, halothane, + epinephrine (1 × 10^{-6} M); **E**, propranolol, halothane, epinephrine, + prazosin (5 × 10^{-7} M).

related to the decreased rate of repolarization. By causing a decrease in SP3 of the action potential, α-adrenergic stimulation would cause impulses evoked during the relative refractory period to be initiated at less negative membrane potentials than under control conditions. Consequently, the V_{max} and conduction velocity of premature impulses initiated in the presence of α-adrenergic stimulation would be reduced.

α-Adrenergic stimulation has been proposed as a primary cause of reentrant arrhythmias during halothane anesthesia, although the exact nature of the arrhythmogenic interaction between α-adrenergic agonists and halothane is unknown (1,8,11). Abbreviated refractoriness and slowed conduction are conducive to the development and maintenance of reentry circuits. The present data suggest that α-adrenergic stimulation may both oppose and potentiate halothane-induced electrophysiologic abnormalities that facilitate reentrant excitation. Whereas halothane decreased the ERP in canine Purkinje fibers, α-adrenergic stimulation prolonged the refractory period. α-Adrenergic stimulation in the presence of halothane actually restored ERP to control levels. Halothane slowed both conduction of impulses initiated at the drive cycle length and conduction of premature impulses in Purkinje fibers. α-Adrenergic stimulation had no effect on the propagation of nonpremature impulses in the presence or absence of halothane; however, α-adrenergic stimulation further delayed conduction of premature impulses in Purkinje fibers exposed to halothane. The combination of halothane and α-adrenergic stimulation might permit development of reentrant circuits if the conduction velocities of premature impulses initiated at short coupling intervals were slow enough to allow reexcitation of a recovered pathway before the arrival of a normal impulse. Knowledge about the combined effects of halothane and α- and β-adrenergic stimulation on refractoriness and on the conduction and initiation of normal and premature impulses might suggest other mechanisms for initiation of arrhythmias, because α_1- and β-adrenoceptor agonists have been shown to interact in a synergistic fashion to produce arrhythmias during halothane anesthesia (8). Electrophysiologic studies using a large number of recording sites and three-dimensional mapping should be performed in intact animals (36), before conclusions are drawn about reentrant and/or nonreentrant mechanisms responsible for the induction of arrhythmias by adrenergic agonists during halothane anesthesia.

We thank Jan Sally and Linda Bednarski for technical assistance.

References

1. Reynolds AK. On the mechanism of myocardial sensitization to catecholamines by hydrocarbon anaesthetics. Can J Physiol Pharmacol 1984;62:183–98.
2. Johnson RR, Eger EI, Wilson C. A comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man. Anesth Analg 1976;55:709–12.
3. Katz RL, Bigger JT. Cardiac arrhythmias during anesthesia and operation. Anesthesiology 1970;33:193–213.
4. Maze M, Smith CM. Identification of receptor mechanism mediating epinephrine induced arrhythmias during halothane anesthesia in the dog. Anesthesiology 1983;59:322–6.
5. Spiss CK, Maze M, Smith CM. α-Adrenergic responsiveness correlates with epinephrine dose for arrhythmias during halothane anesthesia in dogs. Anesth Analg 1984;63:297–300.
6. Maze M, Hayward E, Gaba DM. α_1-Adrenergic blockade raises epinephrine-arrhythmias threshold in halothane anesthetized dogs in a dose-dependent fashion. Anesthesiology 1985;63: 611–5.
7. Tranquilli WJ, Thurman JC, Benson GJ. Alterations in the arrhythmogenic dose of epinephrine after adrenergic blockade with prazosin, metoprolol, or yohimbine in halothane anesthetized dogs. Am J Vet Res 1986;47:114–8.
8. Hayashi Y, Sumikawa K, Tashiro C, Yoshiya I. Synergistic interaction of α_1- and β-adrenoceptor agonists on induction arrhythmias during halothane anesthesia in dogs. Anesthesiology 1988;68:902–7.
9. Hauswirth O. Effects of halothane on single atrial, ventricular, and Purkinje fibers. Circ Res 1969;24:745–50.
10. Atlee JL, Alexander SC. Halothane effects on conductivity of the A-V node and His-Purkinje system in the dog. Anesth Analg 1977;56:378–86.
11. Reynolds AK, Chiz JF. Epinephrine-potentiated slowing of conduction in Purkinje fibers. Res Commun Chem Pathol Pharmacol 1974;9:633–45.
12. Stowe DF, Bosnjak ZJ, Marijic J, Kampine JP. Effects of halothane with and without histamine and/or epinephrine on automaticity, intracardiac conduction times, and development of dysrhythmias in the isolated guinea pig heart. Anesthesiology 1988;68:695–706.
13. Ikemoto Y, Yatani A, Imoto Y, Arimura H. Reduction in the myocardial sodium current by halothane and thiamylal. Jpn J Physiol 1986;36:107–21.
14. Freeman LC, Muir WW III. Effects of halothane on impulse propagation in Purkinje fibers and at Purkinje-muscle junctions: relationship of V_{max} to conduction velocity. Anesth Analg 1991;72:5–10.
15. Turner LA, Bosnjak ZJ, Kampine JP. Actions of halothane on the electrical activity of the Purkinje fibers derived from normal and infarcted canine hearts. Anesthesiology 1987;67:619–29.
16. Niggli E, Rudisuli A, Maurer P, Weingart R. Effects of general anesthetics on current flow across membranes in guinea pig myocytes. Am J Physiol 1989;256:C273–81.
17. Ikemoto Y, Yatani A, Arimura H, Yoshitake J. Reduction of the slow inward current of isolated rat ventricular cells by thiamylal and halothane. Acta Anaesthesiol Scand 1985;29:583–6.
18. Bosnjak ZJ, Kampine JP. Effects of halothane on transmembrane potentials, Ca^{++} transients, and papillary muscle tension in the cat. Am J Physiol 1986;251:H374–81.
19. Terrar DA, Victory JGG. Effects of halothane on membrane currents associated with contraction in single myocytes isolated from guinea-pig ventricle. Br J Pharmacol 1988;94:500–8.
20. Ledda F, Marchetti P, Manni A. Influence of phenylephrine on transmembrane potentials and effective refractory period of single Purkinje fibers of sheep heart. Pharmacol Res Commun 1971;3:195–206.
21. Giotti A, Ledda F, Mannaioni PF. Effects of noradrenaline and isoprenaline, in combination with α- and β-receptor blocking substances, on the action potential of cardiac Purkinje fibers. J Physiol 1973;229:99–113.
22. Rosen MR, Hordof AJ, Ilvento JP, Danilo P. Effects of adrenergic amines on electrophysiological properties and automaticity of neonatal and adult canine Purkinje fibers: evidence for α- and β-adrenergic actions. Circ Res 1977;40:390–400.
23. Rosen MR, Weiss RM, Danilo P. Effect of α-adrenergic agonists and blockers on Purkinje fiber transmembrane potentials and automaticity in the dog. J Pharmacol Exp Ther 1984;231:566–71.
24. Apkon M, Nerbonne JM. α-1 Adrenergic agonists selectively suppress voltage-dependent K^+ currents in rat ventricular myocytes. Proc Natl Acad Sci 1988;85:8756–60.
25. Bruckner R, Scholz H. Effects of α-adrenoceptor stimulation with phenylephrine in the presence of propranolol on force of contraction, slow inward current and cyclic AMP content in the bovine heart. Br J Pharmacol 1984;82:223–32.
26. Miura Y, Inui J, Imamura H. α-Adrenoceptor-mediated restoration of calcium-dependent potential in the partially depolarized rabbit papillary muscle. Naunyn Schmiedebergs Arch Pharmacol 1978;301:201–5.
27. Hartmann HA, Mazzocca NJ, Kleinman RB, Houser SR. Effects of phenylephrine on calcium current and contractility of feline ventricular myocytes. Am J Physiol 1988;255:H1173–80.
28. Shah A, Cohen IS, Rosen MR. Stimulation of cardiac α-receptors increases Na/K pump current and decreases gK via a pertussis toxin-sensitive pathway. Biophys J 1988;54:219–25.
29. Feidida D, Shimoni Y, Giles WR. A novel effect of norepinephrine on cardiac cells is mediated by α-1-adrenoceptors. Am J Physiol 1989;256:H1500–4.
30. Ravens U, Wang X-L, Wettwer E. α-Adrenoceptor stimulation reduces outward currents in rat ventricular myocytes. J Pharmacol Exp Ther 1989;250:364–70.
31. Northover BJ. A comparison of the electrophysiological actions of phentolamine with those of some other antiarrhythmic drugs on tissues isolated from the rat heart. Br J Pharmacol 1983;80:85–93.
32. Dukes ID, Vaughan Williams EM. Electrophysiological effects of α-adrenoceptor antagonists in rabbit sino-atrial node, cardiac Purkinje cells, and papillary muscles. Br J Pharmacol 1984;83:419–26.
33. Burt JM, Spray DC. Adrenergic control of gap junctional conductance in cardiac myocytes. Circulation 1988;78(Suppl): II258.
34. Wickey GS, Larach DR, Schuler HG. Halothane selectively attenuates α_2-adrenoceptor mediated vasoconstriction in rat hindquarter model. Anesthesiology 1988;69:A73.
35. Kenny D, Pelc LR, Brooks HL, Kampine JP, Schmeiling WT, Warltier DC. Alterations of α_1 and α_2 adrenoceptor-mediated pressor responses by halothane and isoflurane anesthesia. Anesthesiology 1989;71:224–34.
36. Pogwizd SM, Corr PB. Reentrant and nonreentrant mechanisms contribute to arrhythmogenesis during early myocardial ischemia: results using three-dimensional mapping. Circ Res 1987;61:352–71.

ANESTH ANALG
1991;72:18–21

Nitrous Oxide Potentiates Succinylcholine Neuromuscular Blockade in Humans

James E. Szalados, MD, François Donati, PhD, MD, FRCPC, and
David R. Bevan, MB, MRCP, FFARCS

SZALADOS JE, DONATI F, BEVAN DR. Nitrous oxide potentiates succinylcholine neuromuscular blockade in humans. Anesth Analg 1991;72:18–21.

Sixty ASA physical status I and II adults received 0.3 mg/kg succinylcholine to determine the effect of prolonged administration of thiopental and that of nitrous oxide on succinylcholine neuromuscular blockade. Succinylcholine was administered either 1 min (group 1) or 6 min (groups 2 and 3) after induction of anesthesia with thiopental. In group 2, anesthesia was maintained with thiopental and the patients' lungs were ventilated with oxygen. In group 3, anesthesia was maintained with only 70% nitrous oxide in oxygen. Train-of-four stimulation of the ulnar nerve was started 30 s before the administration of succinylcholine and repeated every 12 s. The force of contraction of the adductor pollicis muscle was measured. Maximum blockade (mean ± SEM) did not vary significantly between group 1, where thiopental had been administered for 1 min, and group 2, where it had been administered for 6 min (group 1: 61% ± 6%; group 2: 54% ± 8%). However, the addition of nitrous oxide increased neuromuscular blockade (group 3: 80% ± 6%; $P < 0.05$ compared with group 2). The degree of twitch augmentation, i.e., greater than maximal response, and times to twitch augmentation and to maximum blockade did not vary significantly among the groups. It is concluded that nitrous oxide increases succinylcholine neuromuscular blockade and that this is manifest within 6 min. This effect is not due to the duration of the anesthetic because thiopental, administered over a similar time period, did not potentiate succinylcholine.

Key Words: INTERACTIONS (DRUG), SUCCINYLCHOLINE, NITROUS OXIDE. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE—effect of nitrous oxide. ANESTHETICS, GASES—nitrous oxide, interaction with succinylcholine.

The potency of neuromuscular blocking agents is normally measured during stable thiopental-nitrous oxide-narcotic anesthesia. However, in clinical practice the agent used to facilitate tracheal intubation is usually given immediately after the induction agent without the addition of nitrous oxide. Although it is generally assumed that nitrous oxide does not affect the potency of neuromuscular blocking agents, this possibility has not been investigated in humans.

Several estimates of the potency of succinylcholine at the adductor pollicis have been made. Smith et al. (1) reported an ED_{90} of 0.27 mg/kg under thiopental, nitrous oxide, and narcotic anesthesia when succinylcholine was given 5–10 min after induction of anesthesia. However, the same group reported a much higher value of ED_{90} (0.51 mg/kg) when the potency of succinylcholine was tested immediately after thiopental administration, when the equilibrium of nitrous oxide with body tissues was far from complete (2). This last estimate is close to that of Chestnut et al. (3), who reported the results of a study during which succinylcholine was given shortly after induction of anesthesia. There are two possible explanations that could account for the discrepancies among the studies (1–3). First, the duration of anesthesia might affect succinylcholine blockade and, second, nitrous oxide might potentiate the effect of succinylcholine at the neuromuscular junction.

This study was designed to test these two hypotheses. A subparalyzing dose of succinylcholine, 0.3 mg/kg, expected to produce 50%–95% blockade according to the previous estimates (1–3), was given rapidly to three groups of patients. In one group succinylcholine was injected immediately after induction of anesthesia. In the other two groups, succinylcholine was given 5 min after induction of anesthesia

---

Received from the Departments of Anaesthesia, Royal Victoria Hospital and McGill University, Montreal, Quebec, Canada. Accepted for publication August 27, 1990.

Address correspondence to Dr. Donati, Department of Anaesthesia, Room F3.01, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada, H3A 1A1.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

with thiopental at a time when anesthesia was maintained with either thiopental alone or only nitrous oxide in oxygen.

Methods

The protocol was approved by the Hospital Ethics Committee. Sixty adult patients, ASA physical status I or II, scheduled for elective surgery were entered into the study. Patients with hepatic, renal, or neuromuscular disease were excluded. Other exclusion criteria were abnormality of serum electrolyte concentrations, personal or family history of plasma cholinesterase deficiency or malignant hyperthermia, and recent treatment with any medication known or suspected of interfering with neuromuscular function.

On arrival in the operating room, electrocardiogram and pulse oximetry were monitored continuously. Arterial blood pressure was measured noninvasively every 3 min. The left hand and forearm were immobilized in a splint, and the force of contraction of the adductor pollicis was measured. After preoxygenation for 3 min, anesthesia was induced with 5–7 mg/kg thiopental and 1–2 μg/kg fentanyl. Then the patients were randomly assigned to one of three groups. In group 1, 0.3 mg/kg succinylcholine was given 1 min after injection of thiopental while the lungs were ventilated via a mask with 100% oxygen. In group 2, the lungs were also ventilated with oxygen, but 0.3 mg/kg succinylcholine was administered 6 min after thiopental was injected. Incremental doses of thiopental were given, if necessary, to maintain anesthesia. In group 3, 70% nitrous oxide in oxygen was given after induction of anesthesia and 0.3 mg/kg succinylcholine was given 6 min after thiopental. No other intravenous or inhalation agents were given until after maximum levels of neuromuscular blockade had been recorded and the effect of succinylcholine had started to wane. End-tidal carbon dioxide was maintained between 30 and 35 mm Hg, as measured with a mass spectrometer (SARA). After maximum neuromuscular blockade was attained, vecuronium or an additional dose of succinylcholine was given to facilitate tracheal intubation. The rest of the anesthetic management was left to the anesthesiologist's discretion. The succinylcholine given in this study was refrigerated until a few minutes before administration.

In all groups, supramaximal train-of-four stimulation was applied every 12 s to the ulnar nerve at the elbow, starting 30 s before succinylcholine was given. After administration of succinylcholine, the train-of-four response typically showed twitch augmentation, which was most obvious on the first response (T1) and was virtually absent from the fourth response (T4) (1,4). Then neuromuscular blockade became manifest, with T1 usually being greater than T4 because T1 was subject to the phenomenon of twitch augmentation. To avoid the contribution of twitch augmentation, neuromuscular blockade was defined as maximum T4 depression compared with baseline T4 (1). Maximum T1 depression was also measured. In addition, the maximum T1 height or twitch augmentation, the time from injection to maximum twitch augmentation, and the time to maximum twitch depression were measured.

Table 1. Demographic Data (mean ± SEM)

	Group 1	Group 2	Group 3	All
Sex (M/F)	4/16	8/12	8/12	20/40
Age (yr)	55 ± 4	49 ± 4	51 ± 3	52 ± 2
Weight (kg)	67 ± 3	67 ± 3	68 ± 3	67 ± 2
Height (cm)	165 ± 2	169 ± 2	167 ± 1	167 ± 1
Doses				
Thiopental (mg/kg)	6.1 ± 0.4	7.0 ± 0.2	5.7 ± 0.3	6.3 ± 0.2
Fentanyl (μg/kg)	1.5 ± 0.1	1.5 ± 0.1	1.3 ± 0.1	1.4 ± 0.1

The results are presented as mean ± standard error of the mean (SEM). The effect of duration of thiopental anesthesia was assessed by comparing group 1 (succinylcholine given at 1 min) with group 2 (succinylcholine given at 6 min, thiopental-oxygen anesthesia). The effect of nitrous oxide was evaluated by comparing group 2 (oxygen) with group 3 (nitrous oxide). An unpaired Student's *t*-test was used for statistical analysis. Because two simultaneous comparisons were made, the Bonferroni correction was applied. A P value of <0.05 was considered to indicate statistical significance.

Results

There were 20 men and 40 women in the study. Their mean age was 52 ± 2 yr, their mean weight 67 ± 2 kg, and their mean height 167 ± 1 cm. Demographic data are summarized in Table 1. There were no significant differences among the groups, except that the total dose of thiopental was greater in group 2 than in either group 1 or group 3. No cardiovascular changes requiring treatment were observed during the study.

Neuromuscular blockade did not vary according to whether succinylcholine was given 1 min (group 1) or 6 min (group 2) after induction of anesthesia during a thiopental-oxygen anesthetic (Table 2). However, the administration of nitrous oxide (group 3) instead of oxygen (group 2) was associated with more intense

Table 2. Succinylcholine Potency (mean ± SEM)

	Minimum T1 (% control)	Minimum T4 (% control)	Time to onset (s)
Group 1 (O_2, 1 min)	49 ± 8	39 ± 6	131 ± 7
Group 2 (O_2, 6 min)	55 ± 8	46 ± 8	139 ± 10
Group 3 (70% N_2O, 6 min)	26 ± 6	20 ± 6	130 ± 1

O_2, oxygen; N_2O, nitrous oxide.

Table 3. Succinylcholine Twitch Augmentation (mean ± SEM)

	T1 twitch augmentation (% control)	Time to onset (s)
Group 1 (O_2, 1 min)	132 ± 10	58 ± 5
Group 2 (O_2, 6 min)	136 ± 8	65 ± 7
Group 3 (70% N_2O, 6 min)	126 ± 10	54 ± 5

neuromuscular blockade, measured as either T1 or T4 depression (Table 2). Complete abolition of twitch height was seen in two patients in group 1, none in group 2, and six in group 3. The time from injection to maximum blockade was similar in all groups (Table 2). In patients receiving nitrous oxide, end-tidal concentrations of the gas were in the range of 60%–70%, as measured by mass spectrometry, at the time of succinylcholine administration.

The height of T1 reached a maximum value approximately 30% above baseline levels before blockade was established. The magnitude of this twitch augmentation, and the time between injection and maximum twitch augmentation, were similar in all groups (Table 3).

Discussion

This study showed that the neuromuscular effect of a subparalyzing dose of succinylcholine was potentiated by the presence of nitrous oxide. This effect was not caused by an increased duration of the anesthetic inevitably associated with nitrous oxide administration, because the effect of succinylcholine in the presence of nitrous oxide was compared with that of the same dose of relaxant during an anesthetic of the same duration without nitrous oxide. This effect of nitrous oxide, 60%–70% end-tidal concentration, becomes manifest within 5–7 min of its administration. Increasing the duration of a thiopental-oxygen anesthetic by 5 min did not seem to affect the potency of succinylcholine.

The dose of 0.3 mg/kg succinylcholine was chosen to produce measurable neuromuscular blockade in most individuals, i.e., 0% and 100% blocks would be avoided in most circumstances. Previous estimates with nitrous oxide suggested an ED_{90} of succinylcholine of 0.27 mg/kg and an ED_{95} of 0.31 mg/kg (1). Maximum blockade in the present study was 80%, slightly less than in the previous study. The discrepancy would have been even less if logit analysis had been performed, as was the case in the previous dose-response study. Maximum blockade would then average 91%, which is comparable to previous findings (1). Similarly, the maximum blockade in the groups that did not receive nitrous oxide was 54%–61% after 0.3 mg/kg. This is close to the reported ED_{50} (0.27 mg/kg) in a previous study that did not involve nitrous oxide (2). The ED_{50} of succinylcholine with nitrous oxide was reported to be 0.19 mg/kg (1). This suggests that nitrous oxide may decrease succinylcholine requirements by as much as 30%.

A recent study performed in the United Kingdom (3) reported an ED_{50} of 0.31 mg/kg, a finding consistent with the results obtained in the present investigation without nitrous oxide. However, in that study succinylcholine had been left at room temperature for an unspecified time and this might have decreased the apparent potency of the drug. Furthermore, succinylcholine may be less potent in Britain than in North America (5), and electromyographic responses might differ slightly from mechanical responses. However, these two effects may have been counterbalanced by the use of nitrous oxide for an unspecified duration in the British study. Previous estimates suggest that succinylcholine is more potent than indicated in the present study. Cook et al. (6) calculated an ED_{95} of 0.22 mg/kg by extrapolating recovery data back to time zero. This method would tend to underestimate the ED_{90} of a drug that is rapidly metabolized, because substantial metabolism occurs between injection and maximum blockade. Miller et al. (7) reported ED_{90} values of approximately 0.13 and 0.18 mg/kg during isoflurane and halothane anesthesia, respectively. In that study nitrous oxide was also present and blockade was potentiated further by the inhalation agent. Eisenkraft et al. (8) reported an ED_{95} of 0.31 mg/kg with nitrous oxide, but recordings were made from the hypothenar eminence muscles, which may differ from the adductor pollicis in responses to succinylcholine.

The pattern and duration of neuromuscular stimulation before injection of succinylcholine may affect its onset characteristics (9). Maximum blockade might also be altered. Thus, train-of-four stimulation was used in all cases, and it was started at a constant, brief time (30 s) before the injection of succinylcholine.

This method implied that stable baseline train-of-four responses were not obtained before the administration of the relaxant. However, the error involved in the calculation of maximum blockade was probably small because little change in baseline is expected to occur during the short interval (2 min) between injection and maximal blockade. In addition, if an error was introduced, it was systematic for all groups.

The presence of nitrous oxide did not affect the time to maximal blockade. Thus its effect on the factors governing access of succinylcholine to the neuromuscular junction, such as blood flow, is probably small. Similarly, twitch augmentation was of the same magnitude in all three groups. Twitch augmentation is probably the manifestation of repetitive firing, which is the consequence of presynaptic activity (10,11). Exposure to nitrous oxide for 5 min did not appear to alter this phenomenon.

The time-course of nitrous oxide-induced potentiation (5–10 min) is shorter than would be expected if this effect took place in muscle. Calculations suggest that muscle becomes half saturated with nitrous oxide 20–30 min after the start of administration (12). Two alternative mechanisms of action are possible: a central depression causing a decrease in acetylcholine output, thus increasing blockade, and/or inhibition of plasma cholinesterase by nitrous oxide. Irrespective of the mechanism, it can be concluded that succinylcholine is less potent immediately after induction of anesthesia with thiopental than after 6 min of thiopental-nitrous oxide anesthesia.

Succinylcholine is normally given to facilitate tracheal intubation in doses (1–2 mg/kg) that far exceed the ED_{95} reported under nitrous oxide-narcotic anesthesia. These large doses are required because some individuals are relatively resistant to the drug (3), and because some of the muscles that must be relaxed during laryngoscopy and intubation are particularly resistant to succinylcholine (13). This study suggests another reason: the absence of nitrous oxide at induction. Ideally, recommendations for intubating doses of neuromuscular blocking drugs should be based on data obtained without nitrous oxide.

References

1. Smith CD, Donati F, Bevan DR. Dose-response curves for succinylcholine: single versus cumulative techniques. Anesthesiology 1988;69:338–42.
2. Szalados JE, Donati F, Bevan DR. Effect of *d*-tubocurarine pretreatment on succinylcholine twitch augmentation and neuromuscular blockade. Anesth Analg 1990;71:55–9.
3. Chestnut RJ, Healy TEJ, Harper NJN, Faragher EB. Suxamethonium—the relation between dose and response. Anaesthesia 1989;44:14–8.
4. Donati F, Bevan DR. Muscle electromechanical correlations during succinylcholine infusions. Anesth Analg 1984;63:891–4.
5. Katz RL, Norman J, Seed RF, Conrad L. A comparison of the effects of suxamethonium and tubocurarine in patients in London and New York. Br J Anaesth 1969;41:1041–7.
6. Cook DR, Wingard LB, Taylor FH. Pharmacokinetics of succinylcholine in infants, children and adults. Clin Pharmacol Ther 1965;149:113–23.
7. Miller RD, Way WI, Dolan WM, Stevens WC, Eger EI. Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during forane and halothane anesthesia in man. Anesthesiology 1971;35:509–14.
8. Eisenkraft JB, Book WJ, Hahn SM, Papatestas AE, Hubbard M. Resistance to succinylcholine in myasthenia gravis: a dose response study. Anesthesiology 1988;69:760–3.
9. Curran MJ, Donati F, Bevan DR. Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch responses. Br J Anesth 1987;59:989–94.
10. Standaert FG, Adams JE. The actions of succinylcholine on the mammalian motor nerve terminal. J Pharmacol Exp Ther 1965;149:113–23.
11. Hartman GS, Fiamengo SA, Riker WF. Succinylcholine: mechanisms of fasciculations and their prevention by *d*-tubocurarine or diphenylhydantoin. Anesthesiology 1986;65:405–13.
12. Eger EI II. Pharmacokinetics. In: Nitrous oxide N_2O. New York: Elsevier, 1985:81–107.
13. Smith CE, Donati F, Bevan DR. Potency of succinylcholine at the diaphragm and at the adductor pollicis muscle. Anesth Analg 1988;67:625–30.

Steal-Prone Coronary Anatomy and Myocardial Ischemia Associated With Four Primary Anesthetic Agents in Humans

Stephen Slogoff, MD, Arthur S. Keats, MD, Wayne E. Dear, MD, Antonio Abadia, MD, James T. Lawyer, MD, J. Patrick Moulds, MD, and Timothy M. Williams, MD

SLOGOFF S, KEATS AS, DEAR WE, ABADIA A, LAWYER JT, MOULDS JP, WILLIAMS TM. Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. Anesth Analg 1991;72:22–7.

To examine the relationship between myocardial ischemia in patients with steal-prone coronary anatomy and the administration of isoflurane anesthesia, we reviewed coronary angiograms of 955 patients who had participated in a randomized trial of the use of one of four primary anesthetics for coronary artery bypass operations. Steal-prone anatomy was found in 31.8% of patients who had received enflurane; 40.0%, halothane; 32.6%, isoflurane; and 31.7%, sufentanil. Detected by ≥0.1 mV ST segment displacement, ischemia during anesthesia occurred in 290 (30.4%) of all patients with no difference in the incidence among the four primary anesthetics (27.5%–32.9%). Patients with steal-prone anatomy did not suffer more ischemia than patients who needed coronary artery bypass surgery but with other varieties of coronary anatomy. In patients with steal-prone coronary anatomy, the incidence of myocardial ischemia by primary anesthetic was 24.0% with enflurane, 34.4% with halothane, 32.1% with isoflurane, and 38.2% with sufentanil. Systolic blood pressure <90 mm Hg during anesthesia occurred in 416 (45.6%) patients and was twice as common during administration of volatile anesthetics than during that of sufentanil. Hypotension did not increase ischemia frequency in patients with steal-prone anatomy with use of any of the four primary anesthetics including isoflurane. Ischemia was temporally related to hypotension in only 9 patients (0.9%). In none of the 42 patients who had steal-prone anatomy and hypotension during isoflurane anesthesia was ischemia temporally related to hypotension. We conclude that myocardial ischemia is not more commonly associated with isoflurane anesthesia, even in patients with steal-prone coronary anatomy, than with any of the three other primary anesthetics evaluated. Our data do not support restrictions on use of isoflurane in patients with ischemic heart disease.

Key Words: ANESTHETICS, INTRAVENOUS—sufentanil. ANESTHETICS, VOLATILE—enflurane, isoflurane, halothane. HEART, ISCHEMIA—coronary steal. ANESTHESIA, CARDIOVASCULAR—coronary steal.

In 1983 Reiz et al. (1) observed both coronary vasodilation and myocardial ischemia during isoflurane-induced hypotension in 10 of 21 patients with ischemic heart disease undergoing major vascular operations. They postulated ischemia resulted from redistribution of intramyocardial coronary flow described as coronary steal in animal models of coronary artery occlusive disease after administration of coronary vasodilators. In animals with occlusion of one major coronary vessel, both adenosine and dipyridamole induced ischemia by redistribution of coronary flow away from the area of myocardium supplied entirely by collateral circulation (2,3). Ischemia occurred at lesser degrees of coronary vasodilation when the collateral source also had a hemodynamically significant stenosis (4), a configuration now known as "steal-prone coronary anatomy."

Numerous reports have confirmed the potential of isoflurane to produce maldistribution of coronary flow and at times ischemia in animals by this mechanism (5–8). Studies (1,9–12) of isoflurane administered to small groups of patients with coronary artery disease suggested ischemia by isoflurane-induced steal also occurred in humans, particularly when moderate to severe systemic hypotension was also present. In larger groups of anesthetized patients, however, studies of myocardial ischemia failed to

---

Supported in part by grants from Janssen Pharmaceutica, Anaquest Inc., a BOC Health Care Company.

Received from the Division of Cardiovascular Anesthesiology and Department of Cardiology, Texas Heart Institute, Houston, Texas. Accepted for publication August 24, 1990.

Address correspondence to Dr. Slogoff, Cardiovascular Anesthesiology, Texas Heart Institute, P.O. Box 20345, Houston, TX 77225–0345.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

find an incidence of ischemia that is greater with isoflurane than with other anesthetics (13,14). Buffington et al. (15) suggested this failure may result from the pooling of patients with and without steal-prone anatomy. He and his associates estimated that only 23% of patients registered in the multiinstitutional Coronary Artery Surgery Study (CASS) had steal-prone anatomy and that ischemia would not be produced by this mechanism in the other 77%.

In our previous report (13) on the role of primary anesthetic agents in the outcome of coronary artery bypass operations (CABG), we failed to find an incidence of ischemia that is greater in patients given isoflurane than in those given enflurane, halothane, or sufentanil. The configuration of coronary obstructions, particularly steal-prone anatomy, however, was not considered in randomizing patients. The present report describes a blinded review of the angiograms of the patients who participated in that randomized anesthesia trial and the incidence of myocardial ischemia in patients with steal-prone coronary anatomy with and without hypotension associated with four primary anesthetics including isoflurane.

Methods

With Institutional Review Board approval, records of the 1012 patients who participated in the randomized study of primary anesthetic agents were reviewed. Without knowledge of administered anesthetic, occurrence of ischemia, intraoperative course, or outcome, one investigator (W.E.D.) reviewed the coronary angiogram of each patient who participated in the original study for three characteristics: (a) presence of at least one completely occluded major epicardial artery (right, left anterior descending, or proximal circumflex); (b) collateral circulation to the area distal to the completely obstructed vessel from another epicardial artery; and (c) presence of at least 50% obstruction in the vessel supplying collateral circulation. Obstructive lesions were graded by visual estimation based on the average diameter reduction seen in three views.

The views used in this analysis were the left anterior oblique, anteroposterior, and right anterior oblique projection, with cranial or caudal displacement as necessary to place the obstructive lesions in profile. Angiograms were not available in 21 patients who received enflurane; 13, halothane; 9, isoflurane; and 14, sufentanil because the angiograms had been returned to the referring physician. These 57 patients were excluded. From stored data, three characteristics of each patient were tabulated: (a) appearance of electrocardiographic (ECG) ischemia during the period from induction of anesthesia to onset of cardiopulmonary bypass; (b) occurrence of intraoperative hypotension during this period; and (c) lowest systemic blood pressure during the 5 min preceding onset of ischemia. A detailed description of anesthetic management, data acquisition, and analysis is available (13). Patients were randomly assigned to receive enflurane, halothane, isoflurane, or sufentanil. The inhalation drugs were administered in concentrations sufficient to achieve the lower limit of a protocol-defined acceptable systolic blood pressure before tracheal intubation and were administered continuously until start of cardiopulmonary bypass. During the intraoperative period, appropriate treatment for hypertension was instituted whenever systolic blood pressure reached the greater of 20% above mean preoperative systolic pressure or 180 mm Hg; for hypotension, when systolic blood pressure reached the lesser of 20% below mean preoperative systolic blood pressure or 90 mm Hg; and for tachycardia, when heart rate reached the lesser of 20% above mean preoperative rate or 90 beats/min. ST segment displacement unrelated to a treatable hemodynamic change was treated with nitroglycerin.

To assess ECG ST segment displacement, a copy of the preoperative 12-lead ECG (Hewlett Packard model 4700 Pagewriter, sensitivity 1 cm/mV, diagnostic quality 0.05–100 Hz) was obtained for comparison. On arrival in the operating room, tracings of ECG leads II and V_5 calibrated to 1 cm/mV at 25 mm/s for 15 s were recorded every 2 min until initiation of cardiopulmonary bypass. The recording system consisted of Spacelabs Alpha 14 model series 3200 ECG cardule in the monitoring mode (0.5–30 Hz) with recorder model series 2400 (for 50 mm peak-to-peak, DC to 30 Hz ± 1 dB; for 10 mm peak-to-peak, DC to 100 Hz ± 3 dB). Ischemia was diagnosed on calibrated paper recordings as horizontal or downsloping ST segment depression of at least 0.1 mV that extended at least 80 ms beyond the J point of the QRS complex. All data, including the strips of leads V_5 and II, hemodynamic measurements, anesthetic and other drug administrations, and operative events were acquired and recorded by observers not participating in patient care.

After the independent angiogram and record reviews were completed, data for each patient were combined and analyzed by primary anesthetic agent for frequency of steal-prone anatomy, electrocardiographic ischemia, intraoperative hypotension, and temporal relationship of hypotension to ischemia. Frequency data were tested by 2×4 χ^2 analysis and

Table 1. Angiographically Confirmed Coronary Anatomy[a] of Patients Who Randomly Received One of Four Different Primary Anesthetics

Anesthetics	Patients (*n*)	Not completely obstructed coronary and/or no collateral circulation (*n*)	%	Completely obstructed coronary with unobstructed collaterals (*n*)	%	Completely obstructed artery with obstructed collaterals (steal-prone anatomy) (*n*)	%
Enflurane	236	148	62.7	13	5.5	75	31.8
Halothane	240	129	53.8	15	6.2	96	40.0
Isoflurane	239	137	57.3	24	10.0	78	32.6
Sufentanil	240	149	62.1	15	6.2	76	31.7
All patients	955	563	59.0	67	7.0	325	34.0

[a] See text for details.

Table 2. Percent Frequency of Intraoperative Ischemia Among Patients Receiving a Primary Anesthetic by Anatomic Type of Coronary Obstruction

Anesthetic	Not completely obstructed coronary and/or no collateral circulation	Completely obstructed coronary with unobstructed collaterals	Completely obstructed artery with obstructed collaterals (steal-prone anatomy)	All patients
Enflurane	28.4	38.5	24.0	27.5
Halothane	31.8	26.7	34.4	32.5
Isoflurane	32.1	41.7	32.1	32.9
Sufentanil	22.8	33.3	38.2	28.3
All patients	28.6	35.8	32.3	30.4

between pairs by 2 × 2 χ^2 analysis corrected for continuity.

Results

Coronary angiograms were available for 955 (94.4%) of the 1012 patients randomized to receive four primary anesthetic agents in the original study. Angiograms were available for 91.8% of patients who received enflurane; 94.9%, halothane; 96.4%, isoflurane; and 94.5%, sufentanil. Steal-prone coronary anatomy, defined as complete occlusion of one major epicardial artery with collateral circulation provided from another epicardial artery with >50% obstruction, was present in 325 (34.0%) patients (Table 1). Complete occlusion of an epicardial artery with collateral circulation from an unobstructed or <50% obstructed epicardial artery was present in an additional 67 (7.0%) patients. In the remaining 59%, no completely obstructed epicardial vessel was observed or, if complete obstruction were present, no collateral circulation was identified. The distribution of these three varieties of coronary anatomy among the four primary anesthetic groups was not significantly different.

The incidence of intraoperative myocardial ischemia in the entire cohort of 955 patients was 30.4%. Intraoperative ischemia was not more frequent in the steal-prone anatomy group than in the other coronary anatomic groups, nor was ischemia more frequent with any primary anesthetic agent within anatomic groups (Table 2).

Intraoperative hypotension (systolic blood pressure <90 mm Hg) occurred in 416 (43.5%) patients. Hypotension was twice as common during anesthesia with each of the inhalation agents (46.9%–53.8%) than with sufentanil (25.4%), a relationship that applied equally to patients with and without steal-prone anatomy (Table 3). In patients with steal-prone anatomy and hypotension, ischemia appeared in 26%–37% of patients compared with 24%–29% of patients without this anatomy. Differences in rates of ischemia for each primary anesthetic according to anatomic subset were not significant. Ischemia temporally related to hypotension was rare (0.9% of all patients) and not characteristic of any primary anesthetic (Table 3).

Systolic blood pressure <70 mm Hg occurred in 59 (6.2%) patients, ranging from 4.7% (enflurane) to 8.3% (halothane) of patients in each primary anesthetic group. Two of these patients had ischemia temporally related to their hypotension. Ischemia developed in one patient given isoflurane and in one

Table 3. Frequency of Intraoperative Myocardial Ischemia in Hypotensive Patients With and Without "Steal-Prone" Anatomy

	Enflurane	Halothane	Isoflurane	Sufentanil
No steal-prone anatomy				
Patients with intraoperative systolic BP < 90 mm Hg (*n*)	75	81	70	42
Myocardial ischemia in hypotensive patients (*n*)	22 (29)	23 (28)	20 (29)	10 (24)
Myocardial ischemia temporally related to hypotension	1 (1)	3 (4)	1 (1)	1 (2)
Steal-prone anatomy				
Patients with intraoperative systolic BP < 90 mm Hg (*n*)	39	48	42	19
Myocardial ischemia in hypotensive patients (*n*)	10 (26)	17 (35)	14 (33)	7 (37)
Myocardial ischemia temporally related to hypotension	0 (0)	1 (2)	0 (0)	2 (11)

Percentage shown in parentheses.

who received sufentanil when their systemic blood pressures were 50/35 and 54/30 mm Hg, respectively. The sufentanil patient had steal-prone anatomy; the isoflurane patient did not.

Perioperative myocardial infarction occurred in 38 (4.0%) of 955 patients whose angiograms were available for review (range: halothane, 2.9%; enflurane, 5.1% [NS]). Among 325 patients with steal-prone coronary anatomy, infarction occurred in 10 (3.1%) patients (range: isoflurane, 0%; halothane, 6.2% [NS]). In the 57 patients whose angiograms were not available for review, intraoperative ischemia occurred in 20 (35.1%) and did not differ significantly among anesthetics (29%–44%); perioperative infarction occurred in 3 (5.2%).

Discussion

In an editorial commentary, Becker (16) reviewed the data supporting a relationship between isoflurane administration and regional myocardial ischemia induced by a coronary steal mechanism and recommended that use of isoflurane be severely restricted in patients with coronary artery disease. His conclusion was based primarily on data derived from dogs in which partial or complete coronary obstructions were surgically produced as a model of steal-prone anatomy and that were then exposed to isoflurane-induced hypotension (7,8,17). Clinical data supporting his recommendation were limited to one report (1) of ischemia in patients with coronary artery disease in whom ischemia was attributed to the hypotension and coronary dilator actions of isoflurane. Our randomized trial of four primary anesthetic agents in patients undergoing CABG (13) was in progress at the time and subsequently failed to identify an incidence of ischemia greater in patients given isoflurane than in patients given other primary anesthetics. Another larger nonrandomized clinical trial (14) published simultaneously also failed to identify a relationship between isoflurane and intraoperative myocardial ischemia in patients undergoing CABG. Buffington et al. (15) later pointed out that only 23% of the more than 16,000 patients who participated in the multiinstitutional CASS had the specific coronary artery obstructions susceptible to ischemia by isoflurane-induced coronary steal. To date, no data specifically relating the administration of isoflurane to patients with and without coronary steal-prone anatomy in humans are available. Such data would seem essential for documentation of this mechanism of ischemia during isoflurane anesthesia.

This consideration, as well as the desire to learn if the unique ischemia-producing properties of isoflurane were obscured by our failure to account for the varieties of coronary anatomy in our previous study (13), led to the present retrospective analysis. We classified our patients according to three anatomic variants. Among our patients, 59% were considered not to be at risk for ischemia by a steal mechanism because complete occlusion of one vessel was not present or, if complete occlusion were present, no collaterals had developed. These anatomic configurations occurred in 61% of CASS patients (15). Similarly, patients with a completely obstructed coronary artery and with collateral circulation to the affected myocardial region comprised 41% of our population, compared with 39% of the CASS population (15). In our patients, however, 34% had true steal-prone anatomy with >50% obstruction in the vessel supplying the collateral flow, the comparable figure being 23% in CASS patients (15). Considering the larger population and multiinstitutional nature of the CASS compared with our single-institution data of fewer patients, we believe our sample of patients with steal-prone anatomy is a reasonable approximation of the CASS population with regard to this characteristic. The incidence of ischemia in our patients with steal-prone anatomy was not greater during isoflurane anesthesia than during the other primary anesthetics, nor was it greater in patients without steal-prone anatomy.

Data in humans that support the unique relationship of isoflurane and the development of ischemia in patients with coronary artery disease consist of intraoperative experiences of 64 patients described in five reports (1,9–12). Although each patient in these five reports had documented coronary artery disease, the presence of steal-prone anatomy was not documented in any patient. Ischemia appeared during isoflurane anesthesia in 27 (42%) of the 64 patients, a frequency in the same range observed in all our patients regardless of anesthetic administered (13). In most of these 27 patients who suffered ischemia, moderate to profound hypotension (35%–45% reductions in mean arterial pressure) and evidence of myocardial blood flow redistribution accompanied ischemia. Similar systemic and coronary hemodynamic changes, however, occurred in the nonischemic patients. In 6 of these 27 patients, ischemia appeared as a consequence of surgical stimulation or as a continuation of ischemia the onset of which preceded induction of anesthesia (9,10). In three others, ECG ischemia disappeared with onset of surgical stimulation (11). In two other reports (18,19) of isoflurane anesthesia not associated with intraoperative hypotension in 21 patients, ischemia was either reversed or prevented by isoflurane administration. Clearly, these data when considered together do not document a steal mechanism as a cause of ischemia during isoflurane anesthesia, particularly in the absence of a description of coronary anatomy and of the degree of hypotension required to effect ischemia.

Our failure to find myocardial ischemia to be more frequent during administration of isoflurane anesthesia than during that of other general anesthetics for CABG may relate to the low potency of isoflurane as a coronary dilator and to the high frequency of ischemia unrelated to any hemodynamic variable in patients undergoing CABG. Despite the ability of isoflurane to produce coronary steal in animal models, the magnitude of the coronary vasodilation it produces is small, and the adverse effect of decreased supply may be offset by the decreased oxygen demand of myocardial depression also produced by isoflurane. In dogs given isoflurane (1.0 MAC), coronary blood flow increased 26%–29% above mean awake levels (20,21). In the same model, adenosine increased coronary flow 300% above the awake control levels (20), and dipyridamole increased it more than 400% (22). Although some reports (5,7) describe decreased ventricular function owing presumably to ischemia in canine myocardial regions at risk during isoflurane-induced hypotension, others (6,22) find no decrement in function despite evidence of coronary steal. The latter attribute the absence of dysfunction to the protective effect of myocardial depression by isoflurane, an attribute not shared by adenosine or dipyridamole. At the degree of hypotension observed in our patients with steal-prone anatomy, isoflurane may provide this same protective effect by myocardial depression. In addition, ECG ischemia unrelated to any hemodynamic alteration is common in patients with coronary artery disease and occurs spontaneously in the ambulatory state (23), during hospitalization (24), and during operation (13,24). Based on our observations of almost 3000 patients who underwent CABG operations, more than 85% of all intraoperative ischemia was random and unrelated to any hemodynamic abnormality or to the anesthetic administered (13,25–27). In small groups of patients with known coronary artery disease, to attribute ischemia uniquely to the administration of an anesthetic is contrary to the growing body of knowledge concerning perioperative silent myocardial ischemia.

In his exhaustive review of coronary hemodynamics during isoflurane, Priebe (28) was unable to define a relationship between steal-prone anatomy in humans and the occurrence of isoflurane-induced myocardial ischemia. He concluded that isoflurane ". . . is potentially dangerous, in some patients, under some conditions" (28). In this report, we examined at-risk patients, those with steal-prone anatomy, under conditions of isoflurane anesthesia with and without hypotension and found no increased risk of ischemia. Our data support the rarity of patients to whom Priebe's conclusion might apply and fail to support any recommendation for the withholding of isoflurane from patients with any anatomic variant of coronary artery occlusive disease.

References

1. Reiz S, Balfors E, Sorensen MB, Ariola S, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59:91–7.

2. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57: 1103–10.
3. Patterson RE, Kirk ES. Coronary steal mechanisms in dogs with one-vessel occlusion and other arteries normal. Circulation 1983;67:1009–15.
4. Gross GJ, Warltier DC. Coronary steal in four models of single or multiple vessel obstruction in dogs. Am J Cardiol 1981;48: 84–92.
5. Priebe HF, Foex P. Isoflurane causes regional myocardial dysfunction in dogs with critical coronary artery stenoses. Anesthesiology 1987;66:293–300.
6. Tatekawa S, Traber KB, Hantler CB, Tait AR, Gallagher KP, Knight PR. Effects of isoflurane on myocardial blood flow, function, and oxygen consumption in the presence of critical coronary stenosis in dogs. Anesth Analg 1987;66:1073–82.
7. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 1987;66:280–92.
8. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C. Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. Anesthesiology 1987;66:273–9.
9. Larsen R, Hilfiker O, Philbin DM, Sonntag H. Isofluran: Koronardurchblutung und Myokardstoffwechsel bei Patienten mit koronarer Herzkrankheit. Anaesthesist 1986;35:284–90.
10. Moffitt EA, Barker RA, Glenn JJ, et al. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary arterial surgery. Anesth Analg 1986;65:53–61.
11. Reiz S, Ostman M. Regional coronary hemodynamics during isoflurane-nitrous oxide anesthesia in patients with ischemic heart disease. Anesth Analg 1985;64:570–6.
12. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone G, Kettler D. Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 1988;67:936–42.
13. Slogoff S, Keats AS. Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 1989;70:179–88.
14. Tuman KJ, McCarthy RJ, Spiess BD, DaValle M, Dabir R, Ivankovich AD. Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? Anesthesiology 1989;70:189–98.
15. Buffington CW, Davis KB, Gillispie S, Pettinger M. The prevalence of steal-prone coronary anatomy in patients with coronary artery disease: an analysis of the coronary artery surgery study registry. Anesthesiology 1988;69:721–7.
16. Becker LC. Is isoflurane dangerous for the patient with coronary artery disease? (editorial). Anesthesiology 1987;66:259–61.
17. Priebe HJ. Differential effects of isoflurane on regional right and left ventricular performances, and on coronary, systemic, and pulmonary hemodynamics in the dog. Anesthesiology 1987;66:262–72.
18. O'Young J, Mastrocostopoulos G, Hilgenberg A, Palacios I, Kyritsis A, Lappas DG. Myocardial circulatory and metabolic effects of isoflurane and sufentanil during coronary artery surgery. Anesthesiology 1987;66:653–8.
19. Tarnow J, Markschies-Hornung A, Schulte-Sasse U. Isoflurane improves the tolerance to pacing-induced myocardial ischemia. Anesthesiology 1986;64:147–56.
20. Hickey RF, Sybert PE, Verrier ED, Cason BA. Effects of halothane, enflurane, and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart. Anesthesiology 1988;68:21–30.
21. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 1984;63: 557–65.
22. Zimpfer M, Mayer N, Steinbereithner K. Dissimilar effects of isoflurane versus dipyridamole on myocardium supplied by a chronically narrowed coronary artery in the dog. Anesthesiology 1987;67:A587.
23. Deanfield JE, Maseri A, Selwyn AP, Ribeiro P, Chierchia S, Krikler S. Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet 1983;ii:753–8.
24. Knight AA, Hollenberg M, London MJ, et al. Perioperative myocardial ischemia: importance of the preoperative ischemic pattern. Anesthesiology 1988;68:681–8.
25. Slogoff S, Keats AS. Further observations on perioperative myocardial ischemia. Anesthesiology 1986;65:539–42.
26. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.
27. Slogoff S, Keats AS. Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 1988;68:676–80.
28. Priebe HJ. Isoflurane and coronary hemodynamics. Anesthesiology 1989;71:960–76.

ANESTH ANALG
1991;72:28–35

Cardiodynamic Effects of Propofol in Comparison With Thiopental: Assessment With a Transesophageal Echocardiographic Approach

Jan P. Mulier, MD, Patrick F. Wouters, MD, Hugo Van Aken, MD, PhD,
Gery Vermaut, MD, and Eugène Vandermeersch, MD

MULIER JP, WOUTERS PF, VAN AKEN H, VERMAUT G, VANDERMEERSCH E. Cardiodynamic effects of propofol in comparison with thiopental: assessment with a transesophageal echocardiographic approach. Anesth Analg 1991;72:28–35.

In 40 patients, the cardiovascular effects of low- and high-dose propofol anesthesia (single bolus of 1.5 mg/kg in group A, 2.5 mg/kg in group C) were examined and compared with those of low- and high-dose thiopental (4 mg/kg in group B, 6.5 mg/kg in group D) (n = 10 patients per group). After induction of anesthesia with etomidate, all patients were ventilated with 70% nitrous oxide in oxygen. Peripheral arterial systolic blood pressure (SAP) and transesophageal echocardiographic short-axis measurements were used to calculate the end-systolic pressure-volume relationship (E) as an index of global myocardial contractility. In all groups SAP decreased significantly below baseline levels for the duration of the measurements (15 min after drug administration), except for the lower dose of thiopental, where SAP returned to baseline values within 10 min. Propofol at a dose of 1.5 mg/kg significantly decreased cardiac output (CO) (from 5.1 ± 0.25 [mean ± SEM] to 4.2 ± 0.23 L/min), stroke volume (SV) (from 64 ± 3 to 56 ± 3.6 mL), and the slope of E (from 71 ± 3.5 to 65 ± 4.2 mm Hg/mL) until 4 min after drug administration.

The higher dose of propofol significantly decreased CO (from 5.1 ± 0.29 to 4.1 ± 0.26 L/min), SV (from 64 ± 3 to 52 ± 4.6 mL), and the slope of E (from 71 ± 3.6 to 62 ± 3.7 mm Hg/mL) until 10 min after drug administration. End-systolic volume increased significantly (from 60 ± 7.6 to 68 ± 5.5 mL) until the sixth minute, followed by a decrease in end-diastolic volume at 10 min (from 124 ± 6.5 to 118 ± 4.3 mL).

Thiopental at a dose of 4 mg/kg reduced end-diastolic volume significantly at 10 min (118 ± 7.2 versus 128 ± 7.8 mL) and resulted in a significantly higher CO (4.6 ± 0.29 versus 4.2 ± 0.23 L/min) and the slope of E (69 ± 3.9 versus 65 ± 4.2 mm Hg/mL) when compared with low-dose propofol at 4 min. Thiopental at a dose of 6.5 mg/kg significantly reduced the index of afterload (SAP/SV) (from 63 ± 5 to 56 ± 4.6 mm Hg/mL) and the slope of E (from 69 ± 4.2 to 63 ± 3.6 mm Hg/mL), whereas heart rate increased (from 76 ± 5.2 to 84 ± 6.8 beats/min) until the fourth minute after drug administration. When compared with high-dose propofol, end-systolic volume was significantly lower and SAP, SV, CO, and slope of E were significantly higher during thiopental at equipotent doses.

It is concluded that propofol reduces SAP mainly through its negative inotropic properties. Furthermore, the cardiodepressant effects of propofol are more pronounced and more prolonged than those of equipotent doses of thiopental when given as a single bolus.

Key Words: ANESTHETICS, INTRAVENOUS—thiopental, propofol. HEART, CONTRACTILITY—thiopental, propofol.

The induction of anesthesia with propofol (2,6-diisopropylphenol) is often associated with marked decreases in systemic arterial blood pressure in humans (1–4). Clinical investigations have identified a propofol-induced afterload reduction (1,3,4) as the most important factor in explaining propofol-induced reduction of arterial blood pressure. In contrast, a recent study demonstrated that the predominant effect of propofol was a decrease in preload (5). However, Van Aken et al. concluded from their data that propofol might also have negative inotropic properties (2). Recently, data obtained from animal studies have supported this hypothesis (6,7).

In the clinical setting, less invasive monitoring techniques are required to investigate the cardiovascular properties of anesthetic drugs. The ventricular end-systolic pressure-volume relationship, introduced by Sagawa (8), provides a reliable and mini-

---

Received from the Department of Anesthesiology, University Hospitals, Katholieke Universiteit Leuven, Leuven, Belgium. Accepted for publication August 9, 1990.

Address correspondence to Dr. Mulier, Department of Anesthesiology, University Hospitals, Katholieke Universiteit Leuven, Herestraat 49, B-3000 Leuven, Belgium.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

mally invasive technique for measuring myocardial contractility. This method is relatively independent of changes in preload and incorporates afterload changes (9). Inotropic interventions have been shown to modify the slope of the ventricular end-systolic pressure-volume relationship (8,10). This technique is applicable for clinical use provided that peak systolic arterial blood pressure and echocardiographic-derived volume calculations may be substituted for ventricular end-systolic pressure and absolute end-systolic volume, respectively (11).

We have used the end-systolic pressure-volume relationship to determine the effects of a single dose of propofol or thiopental on the myocardial contractility in humans. The purpose of our study was to determine the relative importance of changes in preload, afterload, and myocardial contractility in the propofol-induced decreases in arterial pressure in humans. Thiopental was chosen as the drug of reference and both drugs were used in doses recommended for clinical induction of anesthesia (12,13).

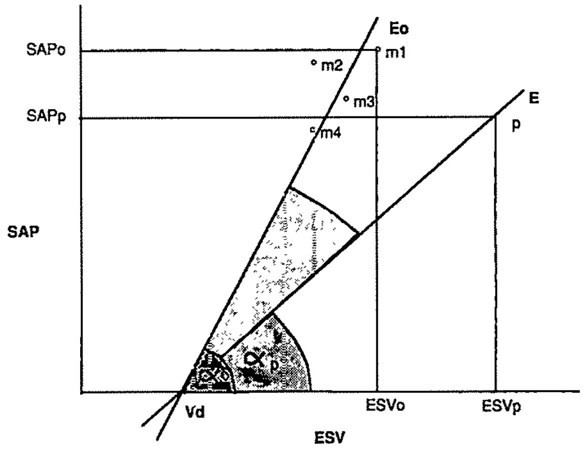


Figure 1. Measurement of *E*: maximal elastance as parameter of contractility. The baseline contractility *Eo* is calculated as a regression line through the points *m1* and *mn*. The change in contractility is reflected by a change in the slope (α) of the line *E* [SAP/(ESV − Vd)] through a new point *p* and the same point *Vd*.

Materials and Methods

Forty ASA physical status I or II patients scheduled to undergo elective major abdominal and orthopedic surgery were studied. The study was approved by the Institutional Ethical Committee, and informed consent was obtained from all patients. Patients did not qualify if they had a history of allergy, were obese (>120% of ideal body weight), or had signs or symptoms of hepatic, renal, hematologic, metabolic, cardiac, or central nervous system disease.

All patients were premedicated 2 h before anesthesia with 2 mg oral lorazepam. On arrival in the operating room, an electrocardiograph was attached and a modified V_5 lead continuously displayed. Under local anesthesia, cannulae were inserted into a peripheral vein and a radial artery. A continuous intravenous (IV) infusion of lactated Ringer's solution was maintained at a rate of 2 $mL \cdot kg^{-1} \cdot h^{-1}$ for the study period. Anesthesia was induced by the IV administration of etomidate (0.3 mg/kg over 60 s). After IV administration of vecuronium (0.1 mg/kg), laryngoscopy was performed, the pharynx and vocal cords were sprayed with 5 mL of a 2% lidocaine solution, and the trachea was intubated. Mechanical ventilation was started, and anesthesia was maintained with 70% nitrous oxide in oxygen. End-tidal P_{CO_2} (P_{ETCO_2}) was monitored using a carbon dioxide analyzer and maintained between 35 and 41 mm Hg using a fixed tidal volume of 10 mL/kg and adjusting the ventilatory rate. Immediately after induction, a transesophageal echocardiograph probe (Hewlett Packard) was introduced into the esophagus to determine the left ventricular volume. The probe was positioned to achieve a cross section of the left ventricle at the midpapillary muscle level and stabilized at the mouth.

The radial arterial pressure and airway pressure tracings, and the electrocardiogram, were simultaneously recorded with a two-dimensional echo view of the heart. Recordings were stored on videotape for later off-line computer analysis. Midpapillary cross-sectional end-diastolic area of the left ventricle and midpapillary cross-sectional end-systolic area of the left ventricle were measured to calculate end-diastolic volume (EDV) and end-systolic volume (ESV) using the modified Simpson formula (14). Stroke volume (SV) was calculated as the difference between EDV and ESV. Cardiac output (CO) was calculated as the product of SV and heart rate (HR). The quotient of systolic arterial blood pressure (SAP) and SV was used as an index of left ventricular afterload as described by Sunagawa et al. (SAP/SV = Ea: effective arterial elastance) (15).

Calculation of Ventricular Contractility With Peak-Systolic Pressure to End-Systolic Volume Relationship

The determination of left ventricular contractility using the principle of the peak-systolic pressure to end-systolic volume relationship (8) was performed as follows (Figure 1). The baseline contractility (*Eo*) was calculated once the patient was hemodynamically stable. Point *m1* had as its coordinates ESV on the x-axis and SAP on the y-axis. Points $m2$ to mn, with the same coordinates, were obtained during the rapid decrease in blood pressure that followed the IV injection of 100 μg nitroglycerin. Measurements were stopped at the moment HR changed. The line Eo was constructed using linear regression analysis of all the points $m1$ to mn. The intercept of the line Eo with the x-axis (point Vd) was the same as the extrapolated left ventricular end-systolic volume at zero blood pressure.

When the drug under investigation was then administered, a new point p with ESV on the x-axis and SAP on the y-axis was determined. The slope of a new line E, drawn through point p and the intercept on the x-axis of the previously determined Eo, point Vd, was then calculated. A change in contractility when compared with baseline was reflected by a change in the slope [SAP/(ESV − Vd)] of line E when compared with Eo. An increase in contractility was reflected by an increase of the slope of E, and a decrease in contractility was reflected by a decrease in the slope of E.

Experimental Protocol

Patients were randomly assigned to four study groups. Fifteen minutes after induction of anesthesia, baseline hemodynamic recordings were obtained and baseline contractility calculated. Group A (10 patients) received a single bolus of propofol in a dose of 1.5 mg/kg. Group B (10 patients) received 4 mg/kg of thiopental. Group C (10 patients) received 2.5 mg/kg of propofol, and group D (10 patients) received 6.5 mg/kg of thiopental. The drugs were administered intravenously over 60 s. Hemodynamic measurements were repeated 2, 4, 6, 10, and 15 min after injection of the drug. Blood samples were drawn at 2, 4, 10, and 15 min after injection of the drug for later analysis of plasma concentrations of the anesthetic drugs.

Data are presented as mean ± SEM. For statistical comparisons of means within a group, the Friedman test was used. For statistical comparison of means between groups A and B, and between groups C and D, the Wilcoxon–Mann–Whitney test was used (16). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

The demographic data of the patients are listed in Table 1. There were no significant differences between groups with regard to age, weight, height, or body surface area.

Table 1. Demographic Data

	Group A	Group B	Group C	Group D
Age (yr)	60 ± 4	62 ± 3	58 ± 4	59 ± 3
Weight (kg)	71 ± 4	76 ± 6	62 ± 4	68 ± 5
Height (cm)	170 ± 3	167 ± 2	171 ± 3	168 ± 4
BSA (m^2)	1.88 ± 0.12	1.77 ± 0.09	1.75 ± 0.08	1.80 ± 0.07

BSA, body surface area.
All values are expressed as mean ± SEM.

The hemodynamic changes associated with each drug are listed in absolute values in Table 2 for groups A and B and in Table 3 for groups C and D. The changes in SAP and E are shown in Figures 2 and 3 for each group. There were no significant differences in baseline values among the four groups.

In all groups SAP decreased significantly below baseline levels. With the low dose of thiopental, SAP returned to baseline values at 10 min; in the other groups SAP remained low for the duration of the experiment (15 min).

At 2 and 4 min, propofol at a dose of 1.5 mg/kg decreased SV (from 64 ± 3 to 59 ± 4.1 and 56 ± 3.6 mL, respectively), CO (from 5.1 ± 0.25 to 4.5 ± 0.37 and 4.2 ± 0.23 L/min, respectively), and the slope of E (from 71 ± 3.5 to 66 ± 3.8 and 65 ± 4.2 mm Hg/mL, respectively). The higher dose of propofol decreased SV (from 64 ± 3 to 52 ± 4.6 mL), CO (from 5.1 ± 0.29 to 4.1 ± 0.26 L/min), and the slope of E (from 71 ± 3.6 to 62 ± 3.7 mm Hg/mL) for 10 min after drug administration. End-systolic volume increased for 6 min (from 60 ± 7.6 to 68 ± 5.5 mL) and returned to baseline at 10 min, whereas EDV decreased at 10 min (from 124 ± 6.5 to 118 ± 4.3 mL).

Thiopental at a dose of 4 mg/kg reduced EDV at 10 min (118 ± 7.2 versus 128 ± 7.8 mL). At 2 and 4 min after drug administration, the higher dose of thiopental increased HR (from 76 ± 5.2 to 82 ± 4.1 and 84 ± 6.8 beats/min, respectively), decreased the slope of E (from 69 ± 4.2 to 62 ± 3.8 and 63 ± 3.6 mm Hg/mL, respectively), and decreased the index of afterload (from 63 ± 5 to 54 ± 3.9 and 56 ± 4.6 mm Hg/mL, respectively). End-diastolic volume was significantly below baseline at 10 min (117 ± 7.2 versus 125 ± 8.6 mL). When compared with thiopental at a dose of 4 mg/kg, 1.5 mg/kg propofol resulted in a significantly lower CO (4.2 ± 0.23 versus 4.6 ± 0.29 L/min) and slope of E (65 ± 4.2 versus 69 ± 3.9 mm Hg/mL) at 4 min after drug administration.

Propofol (2.5 mg/kg) was associated with a lower SAP, CO, slope of E, and SV, and with a higher ESV, when compared with 6.5 mg/kg thiopental. Plasma concentrations of propofol and thiopental are displayed in Figure 4. Both drugs reached their highest

Table 2. Hemodynamic Data (n = 10 in each group) After an Induction Dose (1.5 mg/kg propofol in group A; 4 mg/kg thiopental in group B)

	Baseline	2 min	4 min	6 min	10 min	15 min
Group A						
HR (beats/min)	79 ± 3	76 ± 3.5	75 ± 4.4	78 ± 3.6	79 ± 3	80 ± 3.7
SAP (mm Hg)	112 ± 5.4	95 ± 6.8^a	92 ± 6.6^a	91 ± 6^a	91 ± 7.2^a	95 ± 6.6^a
EDV (mL)	123 ± 5.4	121 ± 6.7	118 ± 6.3	116 ± 4.8	118 ± 6.1	116 ± 5.1
ESV (mL)	59 ± 6.1	62 ± 4.1	62 ± 4.8	60 ± 5.2	59 ± 4.5	57 ± 6.6
SV (mL)	64 ± 3	59 ± 4.1^a	56 ± 3.6^a	56 ± 4.6	59 ± 3.7	59 ± 2.8
CO (L/min)	5.1 ± 0.25	4.5 ± 0.37^a	4.2 ± 0.23^{a,b}	4.4 ± 0.4	4.7 ± 0.29	4.7 ± 0.28
E:SAP/(ESV − Vd) (mm Hg/mL)	71 ± 3.5	66 ± 3.8^a	65 ± 4.2^{a,b}	66 ± 5.8	67 ± 4.7	69 ± 3.9
SAP/SV (mm Hg/mL)	60 ± 3.8	58 ± 4.5	59 ± 3.7	58 ± 5.4	57 ± 4.9	58 ± 4.8
Group B						
HR (beats/min)	75 ± 4.5	76 ± 3.8	79 ± 3.2	76 ± 2.7	76 ± 2.8	75 ± 2.9
SAP (mm Hg)	113 ± 6.4	97 ± 7^a	99 ± 5.4^a	102 ± 6^a	104 ± 6.2	107 ± 7.2
EDV (mL)	128 ± 7.8	126 ± 10.1	119 ± 7.8	120 ± 6.9	118 ± 7.2^a	121 ± 8.1
ESV (mL)	65 ± 3.7	64 ± 4.8	61 ± 4.1	62 ± 5.5	60 ± 4	62 ± 3.7
SV (mL)	63 ± 3.2	62 ± 4	58 ± 3.9	58 ± 3.7	58 ± 3	59 ± 2.9
CO (L/min)	4.7 ± 0.3	4.7 ± 0.34	4.6 ± 0.29^b	4.4 ± 0.26	4.4 ± 0.2	4.4 ± 0.27
E:SAP/(ESV − Vd) (mm Hg/mL)	70 ± 4.7	67 ± 5.1	69 ± 3.9^b	69 ± 4.5	70 ± 4	70 ± 5.2
SAP/SV (mm Hg/mL)	61 ± 5.2	55 ± 4.6	59 ± 3.5	60 ± 4.2	61 ± 5.1	61 ± 3.8

HR, heart rate; SAP, systolic arterial blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; CO, cardiac output; E:SAP/(ESV − Vd), maximal elastance: index of contractility; SAP/SV, arterial elastance: index of afterload.

All values are expressed as mean ± SEM.

$^a P < 0.05$ compared with baseline values within the group.

$^b P < 0.05$ compared with same-time value in the other group.

Table 3. Hemodynamic Data (n = 10 in each group) After an Induction Dose (2.5 mg/kg propofol in group C; 6.5 mg/kg thiopental in group D)

	Baseline	2 min	4 min	6 min	10 min	15 min
Group C						
HR (beats/min)	80 ± 6.9	76 ± 4.8	74 ± 5.7	78 ± 6.2	79 ± 4.6	79 ± 3.4
SAP (mm Hg)	122 ± 5.3	83 ± 2.9^{a,b}	89 ± 4.3^a	88 ± 4.8^a	93 ± 4.6^a	98 ± 5.5^a
EDV (mL)	124 ± 6.5	120 ± 7.5	121 ± 6.8	119 ± 4.6	118 ± 4.3^a	121 ± 7.2
ESV (mL)	60 ± 7.6	71 ± 6.4^{a,b}	68 ± 4.9^{a,b}	68 ± 5.5^{a,b}	66 ± 5.1^b	66 ± 6.7
SV (mL)	64 ± 3	49 ± 4^{a,b}	53 ± 2.6^{a,b}	51 ± 4.3^{a,b}	52 ± 4.6^{a,b}	55 ± 3.2
CO (L/min)	5.1 ± 0.29	3.7 ± 0.34^{a,b}	3.9 ± 0.37^{a,b}	4 ± 0.29^{a,b}	4.1 ± 0.26^{a,b}	4.3 ± 0.24
E:SAP/(ESV − Vd) (mm Hg/mL)	71 ± 3.6	57 ± 3.8^{a,b}	60 ± 4.7^a	60 ± 4.2^{a,b}	62 ± 3.7^a	63 ± 5.3
SAP/SV (mm Hg/mL)	62 ± 4.2	59 ± 3.6	59 ± 5.2	60 ± 4	61 ± 3.5	61 ± 3.6
Group D						
HR (beats/min)	76 ± 5.2	82 ± 4.1^a	84 ± 6.8^a	82 ± 5.9	82 ± 5	79 ± 5.3
SAP (mm Hg)	118 ± 4.7	90 ± 3.8^{a,b}	89 ± 4^a	92 ± 3.5^a	94 ± 3.7^a	98 ± 3.9^a
EDV (mL)	125 ± 8.6	121 ± 9.2	119 ± 8.7	118 ± 6.8	117 ± 7.2^a	118 ± 7.4
ESV (mL)	65 ± 6.2	66 ± 7.8^b	64 ± 5^b	62 ± 6.5^b	60 ± 6.8^b	62 ± 4.9
SV (mL)	60 ± 4	55 ± 2.5^b	55 ± 3^b	56 ± 4^b	57 ± 3.7^b	56 ± 2
CO (L/min)	4.6 ± 0.37	4.5 ± 0.3^b	4.6 ± 0.35^b	4.6 ± 0.28^b	4.7 ± 0.4^b	4.4 ± 0.28
E:SAP/(ESV − Vd) (mm Hg/mL)	69 ± 4.2	62 ± 3.8^{a,b}	63 ± 3.6^a	65 ± 4.8^b	66 ± 5.2	66 ± 5
SAP/SV (mm Hg/mL)	63 ± 5	54 ± 3.9^a	56 ± 4.6^a	59 ± 3.9	59 ± 4.7	60 ± 4

Abbreviations as in Table 2.

All values are expressed as mean ± SEM.

$^a P < 0.05$ compared with baseline values within the group.

$^b P < 0.05$ compared with same-time value in the other group.

concentrations 2 min after injection. These data resemble the profile of redistribution and plasma clearance reported in the literature (13,17). No statistically significant correlations were found between plasma concentrations and hemodynamic variables.

Discussion

Previous studies on the cardiovascular effects of an IV induction dose of propofol in humans have all documented decreases in SAP (2,4,5,17). However, the

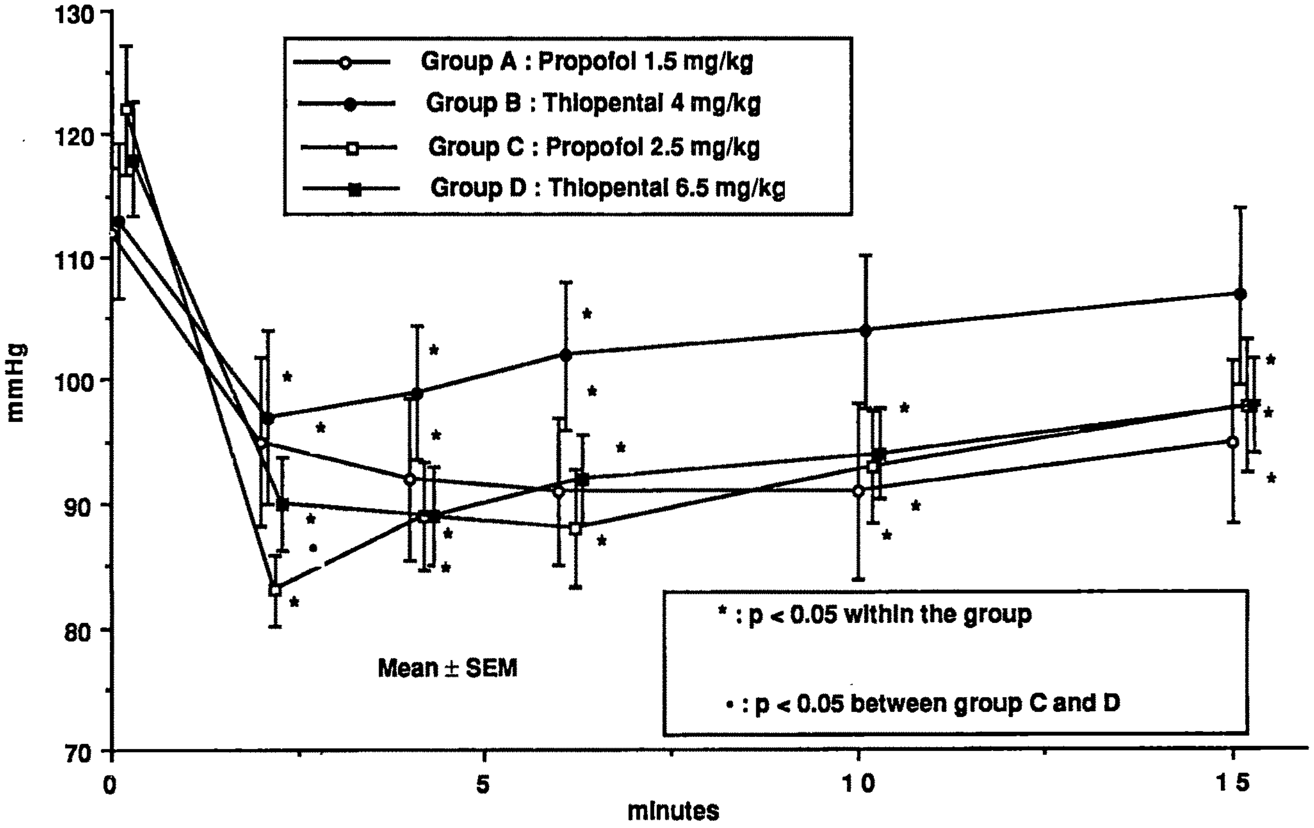


Figure 2. Changes in SAP after single-bolus injections of 4 and 6.5 mg/kg thiopental and 1.5 and 2.5 mg/kg propofol.

reasons proposed as causes for this decrease in blood pressure vary from investigator to investigator. Claeys et al. (4), for example, suggested that the decrease in systemic vascular resistance resulted in a decrease in SAP, while CO and SV remained unchanged. However, experimental conditions such as the presence of hypercarbia in the spontaneously breathing subjects may have accounted for their observations. Van Aken et al. (2) and Carlier et al. (18), however, ascribed the decrease in systemic arterial pressure to significant decreases in CO and SV without concomitant changes in SVR or in pulmonary capillary wedge pressure. Those authors suggested that a negative inotropic action of propofol is responsible for the decrease in CO and SAP. Lepage et al. (5) also found that the decrease in mean arterial pressure was related to a decrease in cardiac index and stroke index (SI). This decrease in cardiac index was associated with a decrease in EDV or preload. They suggested that a decrease in venous return, caused by an increase in venous capacitance, may be responsible for the decrease in CO and systemic arterial pressure. However, whereas mean arterial pressure decreased significantly, ESV remained unaffected in that study. Therefore, a reduction of mean arterial pressure without a decrease in ESV suggests a negative inotropic effect as well.

Recently published results from animal studies provide evidence along the same lines. Brüssel et al. demonstrated, in an acute closed-chest dog model, that propofol reduces the rate of force development in the left ventricle (6). Also, in an open-chest acutely instrumented pig model, Coetzee et al. found a significant reversed correlation between propofol plasma concentrations and myocardial contractility (7); Puttick and Terrar found a shortening of the action potential duration by propofol, indicating a reduction in calcium entry and therefore a possible negative inotropic effect (19).

Our data obtained in humans indicate that the slope of the end-systolic pressure-volume relation (E), as an index of myocardial contractility, decreased significantly during low- and high-dose propofol. End-diastolic volume, as an index of preload, remained stable. Cardiac output decreased consequently and in the presence of an unchanged SAP/SV, as an index of afterload, caused a reduction in SAP.

In agreement with previously published data, the

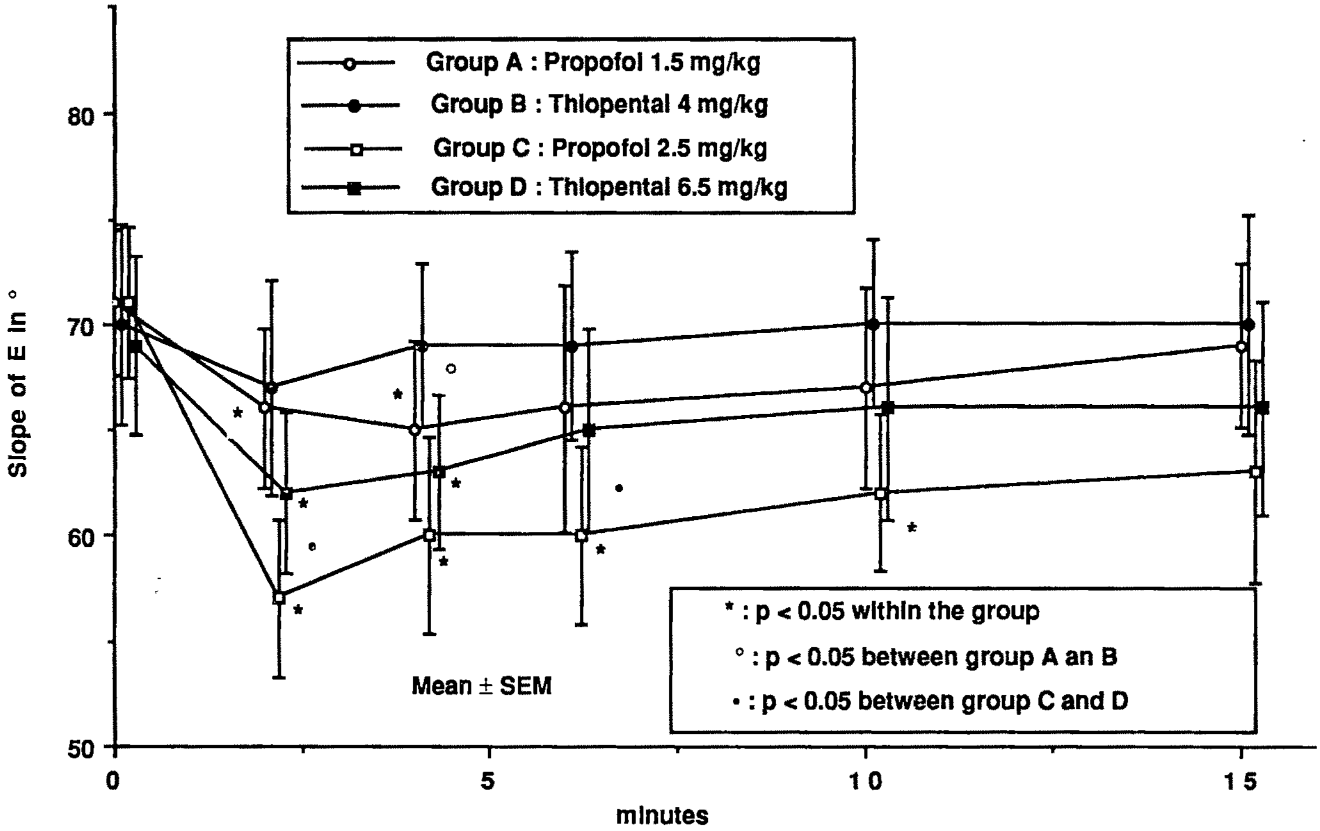


Figure 3. Changes in *E* (mm Hg/mL) as a parameter of contractility after single-bolus injections of 4 and 6.5 mg/kg thiopental and 1.5 and 2.5 mg/kg propofol.

main effect of thiopental in our study was a decrease in afterload (20). The higher dose of thiopental resulted in a decrease in the index of contractility and a delayed decrease in EDV. However, CO remained unchanged due to a compensatory increase in HR and, perhaps, a decrease in SAP/SV. Comparisons with the high dose of propofol indicate that the negative inotropic effects of thiopental are less pronounced.

The reflex tachycardia during thiopental does not occur with propofol in the presence of similar reductions in blood pressure. These findings might indicate more pronounced baroreflex inhibition during propofol anesthesia, as described earlier by Cullen et al. (21).

The peak negative inotropic effect of propofol occurred 2 min after drug administration. However, because the plasma concentrations during non-steady state are not in equilibrium with the tissue levels after single-dose administration, we could not demonstrate a significant correlation between the plasma drug concentrations and hemodynamic measurements. It appears from our data that the hemodynamic effects outlast the hypnotic effects of propofol.

Etomidate as an induction dose of 0.3 mg/kg with 0.1 mg/kg vecuronium was given 15 min before the start of the experiment. Furthermore, 70% nitrous oxide in oxygen was administered throughout the present experiment. We therefore cannot exclude the possibility that these agents modified the hemodynamic or cardiodynamic alterations associated with propofol and thiopental. However, because baseline measurements as well as all measurements after the administration of propofol or thiopental were made under equal anesthetic conditions, it seems likely that the observed changes can be ascribed to the drug that was added. Furthermore, plasma levels of etomidate decline extremely rapidly with a distribution half-life of 2.6 min (22), and in patients without heart disease only minimal effects on the cardiovascular system are observed after IV administration of 0.3 mg/kg etomidate (23). Vecuronium, used to facilitate tracheal intubation and controlled ventilation, has minimal effects on cardiovascular function (24). In the present study all hemodynamic variables returned to baseline levels 10 min after the injection of etomidate and vecuronium.

Comparisons of IV anesthetic agents require the use of equianesthetic doses. Rolly et al. (25) found the relative potency of propofol compared with thiopental to be 1:2.6 in humans (inducing sleep in patients).

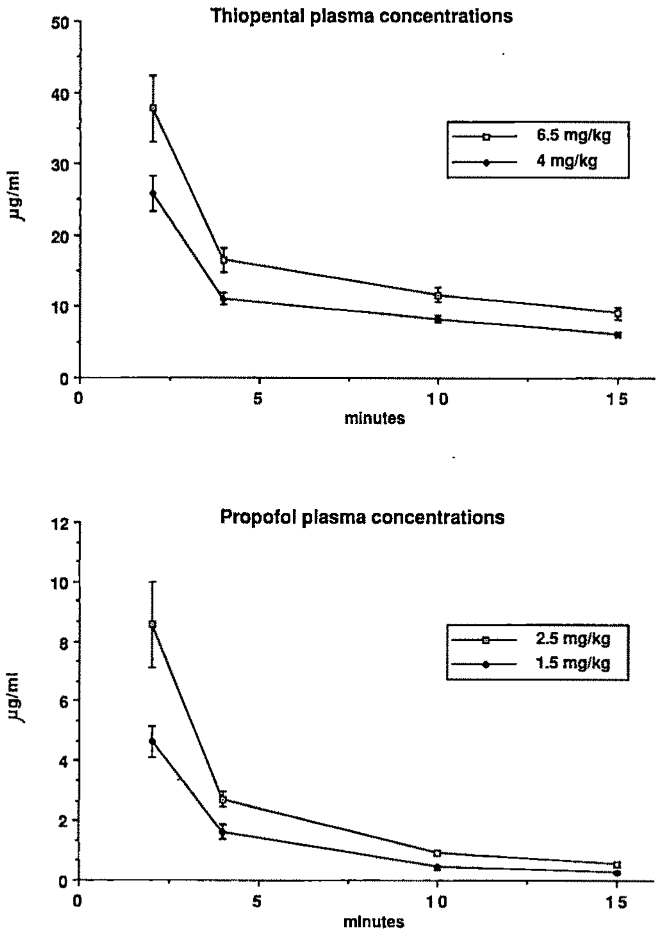


Figure 4. Thiopental and propofol plasma concentrations in micrograms per milliliter at 2, 4, 10, and 15 min after single-bolus injections of 4 and 6.5 mg/kg thiopental and 1.5 and 2.5 mg/kg propofol.

Thus, 1.5 mg/kg propofol corresponds to 4 mg/kg thiopental, and 2.5 mg/kg propofol corresponds to 6.5 mg/kg thiopental.

Assessment of contractility changes in humans in the clinical setting is quite difficult. Although radionuclide ventriculography with a gamma camera of small size and true mobility permits semi-invasive pharmacodynamic studies, problems such as difficulty in obtaining absolute volumes (as a result of the fixed field view of the detector), probe positioning over the left ventricle, recording of background activity, and radiation safety in the operating room make the use of this technique less practical (26,27).

Changes in the maximum rate of increase in left ventricular pressure (dP/dt_{max}) are known to be highly sensitive to acute changes in contractility. Although measurement of left ventricular dP/dt may be used to study anesthetic drugs, provided that high-fidelity catheter-tip manometers are used, this technique is very invasive. Also, dP/dt_{max} is dependent on preload, afterload, and HR. Furthermore, due to ethical considerations this method cannot be used to obtain information about the effects of anesthetics on left ventricular contractility in humans. Therefore, the less invasive method using the pressure-volume analysis was used in this study.

Determination of true end-systolic pressure requires left ventricular or aortic pressure measurement. The manipulation of arterial pressure to obtain different pressure-volume points may cause reflex inotropic changes because of sympathetic activation or withdrawal. Thus, for clinical use this relationship needs simplification; this was described by Heinrich et al. (11). Several important features of our protocol have to be explained. First, cross-sectional areas of the ventricle can be measured, which provides a more accurate estimation of ventricular volume than do diameter measurements. Lunkenheimer et al. (28) showed that contraction is mainly concentric and that the long-axis measurement is relatively stable. Hence, calculations are made with one long-axis measurement using the change in cross-sectional area. Second, sympathetic stress and changes due to respiration have to be avoided throughout the experiment. Therefore, our patients were anesthetized with etomidate as induction agent and 70% nitrous oxide in oxygen as a maintenance anesthetic. Furthermore, they were paralyzed, and ventilation was controlled. Intubation, changes in respiration, and probe positioning were performed immediately after administration of etomidate. Baseline measurements were obtained 15 min after the induction of anesthesia during 70% nitrous oxide in oxygen and were immediately followed by administration of the drug under investigation.

In conclusion, our end-systolic pressure-volume relationship model demonstrates that propofol has dose-dependent, negative inotropic properties in humans. Furthermore, it is shown that the negative inotropic properties of propofol outweigh those of equipotent doses of thiopental in both intensity and duration.

References

1. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The hemodynamic effects of intravenous induction. Anaesthesia 1985;40:735–40.
2. Van Aken H, Meinshausen E, Prien T, Brüssel T, Heinecke A, Lawin P. The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N_2O in humans. Anesthesiology 1988;68:157–63.
3. Coates DP, Christopher RM, Prys-Roberts C, Turtle M. Hemodynamic effects of infusions of the emulsion formulation of

propofol during nitrous oxide anesthesia in humans. Anesth Analg 1987;66:64–70.

4. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988;60:3–9.
5. Lepage JM, Pinaud ML, Hélias JH, et al. Left ventricular function during propofol and fentanyl anesthesia in patients with coronary artery disease: assessment with a radionuclide approach. Anesth Analg 1988;67:949–55.
6. Brüssel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken H, Lawin P. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. Anesth Analg 1989;69:35–40.
7. Coetzee A, Fourie P, Coetzee J, et al. Effect of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. Anesth Analg 1989;69:473–83.
8. Sagawa K. The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use. Circulation 1981;63:1223–7.
9. Suga H, Sagawa K, Shoukas A. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 1973;32:314–22.
10. Grossman W, Braunwald E, Mann T, McLaurin LP, Green LH. Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations. Circulation 1977;56: 845–52.
11. Heinrich H, Fösel Th, Fontaine L, Spilker D, Winter H, Ahnefeld FW. Assessment of contractility changes in humans by transoesophageal echocardiography: the peak-systolic pressure end-systolic diameter relationship. Int J Clin Monit Comp 1987;4:243–8.
12. Fahy LY, van Mourik GA, Utting JE. A comparison of the induction characteristics of thiopentone and propofol. Anaesthesia 1985;40:939–44.
13. White PF. Propofol: pharmacokinetics and pharmacodynamics. Semin Anesth 1988;7(Suppl):4–20.
14. Gueret P, Meerbaum S, Wyatt HL, Zwehl W, Corday E. Determination of left ventricular stroke volume by cross-sectional echocardiography. Circulation 1979;60:1104–13.
15. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245:H773–80.
16. Siegel S, Castellan NJ. Singapore: McGraw Hill, 1988. Nonparametric statistics for the behavioral sciences, 2nd ed.
17. Christensen JH, Andreasen F, Jansen JA. Pharmacokinetics and pharmacodynamics of thiopentone. Anaesthesia 1982;37: 398–404.
18. Carlier S, Van Aken H, Vandermeersch E, Thorniley A, Byttebier G. Does nitrous oxide affect the hemodynamic effects of anesthesia induction with propofol? Anesth Analg 1989;68: 728–33.
19. Puttick RM, Terrar DA. Effects of propofol on membrane currents and contraction in single myocytes isolated from guinea-pig ventricle. Br J Pharmacol 1989;98:742R.
20. Flickinger H, Fraimow W, Cathcart R, Nealon T. Effect of thiopental induction on cardiac output in man. Anesth Analg 1961;40:693–700.
21. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effects of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987;66:1115–20.
22. Van Hamme MJ, Ghoneim MM, Ambe JJ. Pharmacokinetics of etomidate, a new intravenous anesthetic. Anesthesiology 1978; 49:274–7.
23. Brückner JB, Gethmann JW, Patschke D, Tarnow J, Weymar A. Untersuchungen zur Wirkung von Etomidate auf den Kreislauf des Menschen. Anaesthesist 1974;23:322–30.
24. Morris RB, Cahalan MK, Miller RD, Wilkinson PL, Quasha AL, Robinson SL. The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 1983;58:438–40.
25. Rolly G, Versichelen L. Comparison of propofol and thiopental for induction of anaesthesia in premedicated patients. Anaesthesia. 1985;40:945–8.
26. Berger HJ, Davies RA, Batsford WP, Hoffer PB, Gottschalk A, Zaret BL. Beat to beat left ventricular performance assessed from the equilibrium cardiac blood pool using a computerized nuclear probe. Circulation 1981;63:133–41.
27. Tarnow J. Clinical possibilities and limitations of techniques assessing the effects of anaesthetics on myocardial function. Br J Anaesth 1988;60:52S–7S.
28. Lunkenheimer PP, Redmann K, Whimster WF, Theissen J, Frieling G, Lunkenheimer A. The problem created by myocardial structure in assessing function. Br J Anaesth 1988;60:2S–7S.

ANESTH ANALG
1991;72:36–47

A Blinded Comparison of Noninvasive, In Vivo Phosphorus Nuclear Magnetic Resonance Spectroscopy and the In Vitro Halothane/Caffeine Contracture Test in the Evaluation of Malignant Hyperthermia Susceptibility

Jeffrey Olgin, MD, Henry Rosenberg, MD, Gregory Allen, MD, FRCPC, Richard Seestedt, BA, and Britton Chance, PhD

OLGIN J, ROSENBERG H, ALLEN G, SEESTEDT R, CHANCE B. A blinded comparison of noninvasive, in vivo phosphorus nuclear magnetic resonance spectroscopy and the in vitro halothane/caffeine contracture test in the evaluation of malignant hyperthermia susceptibility. Anesth Analg 1991;72:36–47.

Malignant hyperthermia (MH) is a potentially fatal, anesthetic-induced syndrome. Currently, the only accurate means of diagnosing susceptibility to this syndrome is the testing of biopsied skeletal muscle for its contracture response to halothane and caffeine. A less invasive means of diagnosis is needed. The authors previously reported that MH-susceptible patients studied by in vivo phosphorus nuclear magnetic resonance (^{31}P NMR) spectroscopy demonstrated a higher resting inorganic phosphate (Pi) to phosphocreatine (PCr) ratio in their skeletal muscle, as well as a slower postexercise recovery of PCr/Pi, when compared to normal controls. In the present blinded study, the authors compared in vivo ^{31}P NMR determination of resting Pi/PCr and recovery rate of PCr/Pi in forearm muscles to in vitro halothane/caffeine contracture test results in 42 patients. Forty-three control subjects were studied to establish normal NMR values of resting Pi/PCr and recovery rate of PCr/Pi. Their findings were compared with those of 27 patients shown to be MH-susceptible and 15 patients MH-negative by contracture testing. The MH-susceptible group had a significantly ($P < 0.005$) higher resting Pi/PCr value (0.202 ± 0.044) than either the MH-negative (0.152 ± 0.043) or the control (0.141 ± 0.026) group. The MH-susceptible group also had a significantly ($P < 0.02$) slower postexercise recovery rate of PCr/Pi (1.50 ± 0.872 $PCr \cdot Pi^{-1} \cdot min^{-1}$) than either the MH-negative (2.11 ± 1.07 $PCr \cdot Pi^{-1} \cdot min^{-1}$) or control (2.25 ± 0.828 $PCr \cdot Pi^{-1} \cdot min^{-1}$) group. Twenty-six of the 27 MH-susceptible patients demonstrated abnormal NMR test results (a resting $Pi/PCr \geq 0.18$ or recovery rate < 1.0 $PCr \cdot Pi^{-1} \cdot min^{-1}$), and 13 of the 15 MH-negative patients had normal NMR results. Although neither NMR parameter alone was diagnostically reliable, an NMR test utilizing both parameters was quite accurate. The NMR test and contracture test demonstrated an overall agreement of 93% with a copositivity of 96% and conegativity of 87%. The sensitivity and specificity of the NMR test is estimated to be 98.8% ± 11.8% and 95.3% ± 20.3%, respectively. The role of ^{31}P NMR in the diagnosis of MH susceptibility and possible mechanisms underlying the observations are discussed.

Key Words: HYPERTHERMIA, MALIGNANT—diagnosis of susceptibility.

Malignant hyperthermia (MH) is an anesthetic-induced syndrome that is potentially fatal (1). Susceptibility to MH is inherited. The clinical syndrome is classically characterized by hyperthermia, muscle rigidity, cardiac arrhythmias, rhabdomyolysis, hyperkalemia, and acidosis, most frequently in response to halothane and succinylcholine (1,2). It has, however, been reported after other inhalation anesthetics and may have a less fulminant presentation, especially if the duration of exposure is brief (2). This acute syndrome is due to a hypermetabolic state of skeletal muscle and the resultant physiologic response (1,3,4).

Supported by the Hahnemann Anesthesia Research Fund.

Received from the Department of Internal Medicine, University of California San Francisco, San Francisco, California; the Department of Anesthesiology, Hahnemann University Hospital, Philadelphia, Pennsylvania; and the Department of Biochemistry and Biophysics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. Accepted for publication August 10, 1990.

Work performed at the Magnetic Resonance Spectroscopy Center, Department of Biochemistry and Biophysics, University of Pennsylvania School of Medicine; and the Laboratory for the Study of Malignant Hyperthermia, Department of Anesthesiology, Hahnemann University.

Address correspondence to Dr. Rosenberg, Department of Anesthesiology, Hahnemann University Hospital, Mail Stop 310, Broad and Vine Streets, Philadelphia, PA 19102-1192.

©1991 by the International Anesthesia Research Society

Table 1. Muscle Disorders That Have Been Shown to Have Abnormalities by ^{31}P NMR

Elevated Pi/PCr ratios
1. Mitochondrial myopathies (8)
2. Metabolic myopathies (glycolytic defects, lipid storage diseases) associated with secondary atrophy (9,10)
3. Muscular and myotonic dystrophies (10–12)
4. Polymyositis (10,17)
5. Hypothyroid myopathy (13)
6. Advanced denervating muscle disorders (10,14)
7. Muscle injury (15)
8. Malignant hyperthermia (7)

Slow postexercise recovery rate
1. Mitochondrial myopathies (8)
2. Malignant hyperthermia (7)

Numbers in parentheses indicate related references.

A fatal outcome can be prevented in these patients if their susceptibility is known before their receiving anesthesia and surgery. However, because the signs and symptoms of MH are present only during anesthesia, preoperative diagnosis of susceptibility is difficult. A personal or family history of possible MH raises suspicion, but is not diagnostic of susceptibility. Findings of subclinical myopathy may be present in the history or on physical examination, but are nonspecific (5).

The halothane/caffeine contracture test is the most widely accepted means of confirming susceptibility (6). Although the contracture test is specific, it requires an open-muscle biopsy, carrying with it the inconvenience, morbidity, risks, and costs of any surgical procedure. For this reason, efforts have been made to develop a less invasive means of determining MH susceptibility (4,6).

Phosphorus nuclear magnetic resonance (^{31}P NMR) spectroscopy is a technique that has recently been suggested as a possible means of diagnosing MH susceptibility (4,7). It is a noninvasive method for determining intracellular changes in high-energy phosphates. The technique has been widely used to study various muscle disorders (Table 1) (7–17).

Prompted by the results of in vitro and in vivo ^{31}P NMR studies of muscles in MH-prone swine during MH episodes, we conducted a pilot study of humans to determine whether in vivo ^{31}P NMR could detect abnormalities in MH-susceptible patients when they were not in an acute episode (7). In studying 13 MH-susceptible individuals we found that these patients, when not challenged with an anesthetic, had a significantly higher muscle inorganic phosphate (Pi) to phosphocreatine ratio (PCr) at rest, as well as a slower postexercise recovery of PCr/Pi, than did normal and MH-negative controls (7). These results led us to conclude that ^{31}P NMR may have a role in the noninvasive diagnosis of MH susceptibility. We here report a larger, blinded, follow-up study comparing the ^{31}P NMR test with the in vitro halothane/caffeine contracture test in the evaluation of MH susceptibility to determine its effectiveness as a noninvasive diagnostic tool in this disease.

Table 2. Indications for Muscle Biopsy Testing in the Study Population

Indication	No. of patients	Percent of total patients
Family history	30	66.7
Relative with MH or suspicious episode	30	66.7
Relative with positive contracture test	14[a]	31.1
Symptoms during anesthesia	14	31.1
MH reaction	3[b]	6.7
Suspicious episode[c]	5	11.1
Masseter muscle rigidity	6	13.3
Persistently elevated resting serum creatine kinase	1	2.2

MH, malignant hyperthermia.

[a] Patients also had a relative who had had an MH or suspicious episode.

[b] These patients did not undergo biopsy, but were studied by NMR.

[c] This includes some, but not necessarily all, of the following signs during anesthesia: elevated temperature, muscle rigidity, arrhythmia, increased end-tidal CO_2, acidosis, and hyperkalemia.

Methods

Subjects

Forty-five patients referred to the Hahnemann University MH Diagnostic Center were studied. Subjects (26 male and 19 female) were between 5 and 64 yr old; two were under 10 yr of age. The indications for muscle contracture testing in the study population are summarized in Table 2. Thirty patients had a family history of MH. Fourteen patients had symptoms during previous anesthesia; three of these had had a documented MH episode. One patient had no personal or family history of MH but was tested because of persistently elevated serum creatine kinase (CK) levels. Forty-three healthy, normal control subjects (24 males and 19 females) between 18 and 60 yr of age were studied only by NMR. Informed consent was obtained from all participants.

Human Muscle Biopsy and Contracture Testing

All but three of the patients underwent muscle biopsy for contracture testing and histologic staining.

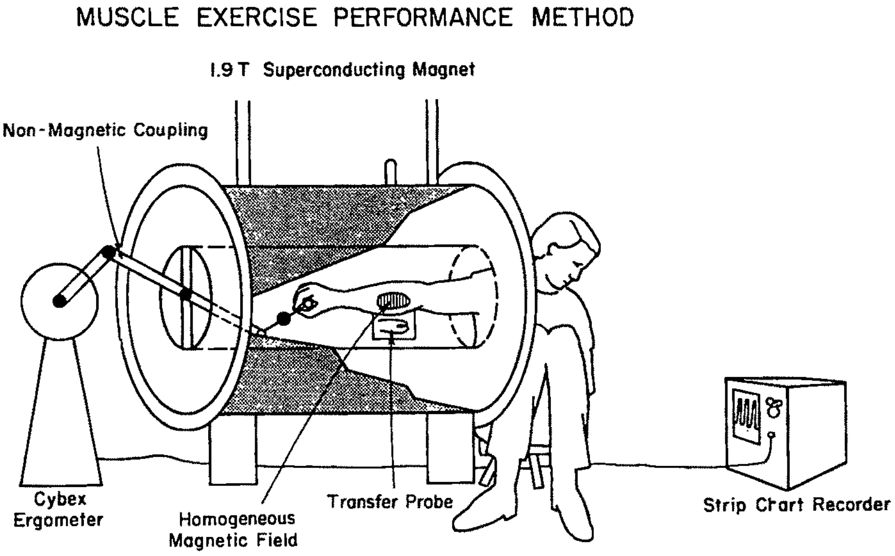

MUSCLE EXERCISE PERFORMANCE METHOD
1.9 T Superconducting Magnet
Non-Magnetic Coupling
Cybex Ergometer
Homogeneous Magnetic Field
Transfer Probe
Strip Chart Recorder

Figure 1. In vivo forearm muscle testing by ^{31}P NMR. The patient's forearm was placed on the probe in the magnet such that the wrist flexors were centered over the coil. A handle connected to a Cybex ergometer was used for exercise. Force of contraction was displayed on the strip chart recorder.

The three patients who did not undergo biopsy had had documented MH episodes (more than 1 yr before NMR testing) defined as elevated temperature, muscle rigidity, tachycardia, acidosis, and rhabdomyolysis during halothane anesthesia and resolution of these signs after dantrolene. In addition, these patients had biopsy-proven MH-susceptible relatives. These three patients are included in the population distributions as MH-susceptible, but were not included in any comparison between NMR and the contracture test.

Open surgical biopsies of the vastus lateralis were performed under femoral and lateral femoral cutaneous nerve blocks. The muscle specimens were transported at room temperature in Krebs–Ringer solution (composed of 118 mM NaCl, 3.4 mM KCl, 0.8 mM $MgSO_4$, 1.2 mM KH_2PO_4, 11.1 mM glucose, 25.0 mM $NaHCO_3$, and 2.5 mM $CaCl_2 \cdot 6H_2O$) with pH adjusted to 7.4. The procedure for contracture testing at the Hahnemann University MH Diagnostic Center has been described in detail elsewhere (18–20). The muscle specimens were divided into strips measuring 0.5–3.0 cm × 2.0–5.0 mm × 1.0–3.0 mm and mounted to a force transducer in a 5.0-mL tissue bath containing Krebs' solution at 37°C bubbled with carbogen (95% O_2, 5% CO_2). The length of each muscle strip was adjusted to the optimum resting tension derived from its length-twitch tension curve. The strips were supramaximally stimulated with 2-ms electrical pulses at a frequency of 0.2 Hz.

After a 30-min equilibration period, three muscle strips from each patient were exposed to 3% halothane in carbogen bubbled through the tissue bath for 5 min. The halothane concentration in the gas phase was determined by gas chromatography. A contracture response of $\geq$0.7 g in any strip was considered abnormal. A contracture of 0.7–0.8 g is an equivocal response, but was considered a positive result (only one patient had a response in this range).

Three other muscle strips from each patient were equilibrated for 30 min, then exposed to incremental doses of caffeine (0.5–32 mM), added to the bath in twofold increments. A contracture of 0.3 g or more to 2 mM of caffeine was considered abnormal.

Muscle samples were also sent to pathology for routine histologic and histochemical evaluation (including hematoxylin and eosin; trichrome; NAD ATPase at pH 4.3, 4.6, 9.4; acridine orange; orotidine; acid phosphatase; succinate dehydrogenase; and periodic acid-Schiff).

Phosphorus Nuclear Magnetic Resonance Spectroscopy

The basic protocols and techniques used at the University of Pennsylvania Magnetic Resonance Spectroscopy Center for testing human arm muscle by NMR have been detailed in previous publications (21–23). Only a brief description will be presented here.

Nuclear magnetic resonance spectra of the wrist flexor muscles were obtained using a double-tuned, 4-cm-diameter, two-turn surface coil. Subjects were tested in a 1.9-T, 30-cm-bore magnet, as shown in Figure 1, coupled to a spectrometer (Otsuka Electronics) with an operating frequency of 32.5 MHz for phosphorus. Radiofrequency pulses of 45-μs duration (90° flip angle) were delivered every 5 s for NMR acquisition. This pulse pattern gives partially saturated spectra of 81% for PCr, 86% for Pi, and 91% for β-adenosine triphosphate of fully relaxed spectra obtained with a pulse delay of 20 s (7). The short interpulse delay was used to average quickly the rapidly changing concentrations of metabolites during exercise and recovery.

Spectra were obtained during rest, exercise, and postexercise recovery. Resting spectra were averaged over 5–10 min, depending on the signal-to-noise ratio obtained. The longer averaging times were sometimes needed to obtain a higher signal-to-noise ratio to allow accurate analysis of the spectrum. After the collection of resting data, each subject began an exercise protocol. This consisted of wrist flexions of 0.5-s duration to push repeatedly a handle connected to a Cybex ergometer (as shown in Figure 1) once every 5 s, just after NMR sampling (21). First, the subject's maximum voluntary contraction (MVC) against the ergometer was determined. Each subject then progressively exercised, first at 20% of their MVC for 4 min, then at 40% MVC for at least 4 min until the PCr and Pi peak heights were roughly equal to each other (i.e., Pi/PCr = 1, by peak heights) for at least 2 consecutive minutes. If this was not obtained at 40% of MVC, exercise was progressively increased to 60% MVC and 80% MVC until the peak heights were equal. At the end of exercise, recovery was followed for 4 min in 1-min blocks. Recovery data were not obtained in five patients and eight controls either because of age (difficulty following directions) or poor signal-to-noise levels. Resting spectra were obtained from all patients and subjects.

The spectra were multiplied by 5-Hz line broadening, Fourier transformed, phased, and plotted with an *x-y* plotter. A common baseline for all peaks was determined, and peak areas for Pi and PCr were obtained by triangulation to obtain ratios of Pi/PCr. Intracellular pH was determined from the chemical shift of Pi from PCr (15,24).

Data Analysis

Analysis of NMR data and contracture test results was carried out in a blinded fashion by independent investigators and confirmed by one other investigator. Data analysis was performed without knowledge of the patient's diagnosis or to which group he or she belonged (control or patient). Based on the results of his or her contracture test, as described above, it was determined whether a patient was in the MH-susceptible or the MH-negative group. Wilcoxon's rank-sum test was used for statistical analysis of differences between the two populations. All values are reported as mean ± SD.

Table 3. In Vitro Halothane/Caffeine Contracture Test Results

Response	No. of patients
Positive	27
0.7–0.8 g (halothane)	1
≥0.8 g (halothane)	26
≥0.3 g (caffeine)[a]	5
Negative	15
<0.7 g (halothane) and <0.3 g (caffeine)	
Total	42

[a] All patients with a positive caffeine contracture response also had a positive halothane contracture response.

Abnormality in the NMR test was determined from the distributions of resting Pi/PCr and recovery rate of PCr/Pi for patients determined to be either MH-susceptible or MH-negative by halothane/caffeine contracture testing. This was accomplished by the use of receiver operating characteristic (ROC) curves, as described in Results.

Because of the difficulty in obtaining an accurate diagnosis of MH susceptibility in most patients (the only way to do so is to observe an MH episode during anesthesia), the NMR test was directly compared with the halothane/caffeine contracture test. The methods described by Buck and Gart for comparing a screening test and a reference test, with the contracture test as the reference test, were used to obtain estimates of sensitivity and specificity for the NMR test (25,26).

Results

The contracture tests (Table 3) revealed that 27 patients were MH-susceptible and 15 patients were MH-negative. None of these patients had clinical evidence of muscle disease, and the histologic findings were not specific enough to suspect a diagnosis of any myopathy in any of them. There was no correlation between histologic findings and NMR results. In addition, there were three patients who did not have biopsies taken but who both had had documented MH episodes and had relatives who tested positive by contracture testing. These three patients were not used in the comparisons between NMR and the contracture test (i.e., in the calculation of sensitivity and specificity).

Phosphorus nuclear magnetic resonance spectra obtained during rest from an MH-susceptible and an

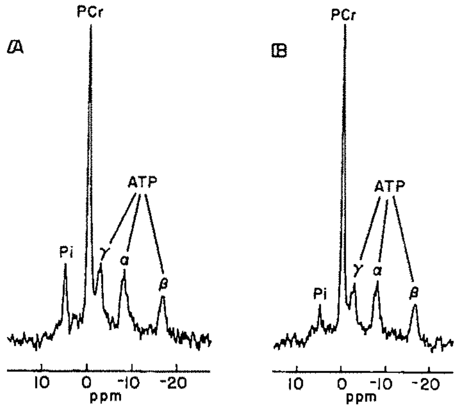


Figure 2. Phosphorus nuclear magnetic resonance spectra of forearm muscles from an MH-susceptible (A) and an MH-negative (B) patient. The vertical scale has been adjusted such that the PCr peaks are equal in height. The different peaks represent relative amounts of phosphorus nuclei from different high-energy phosphate compounds, as labeled. α, β, δ-ATP, the three phosphates of adenosine triphosphate (ATP).

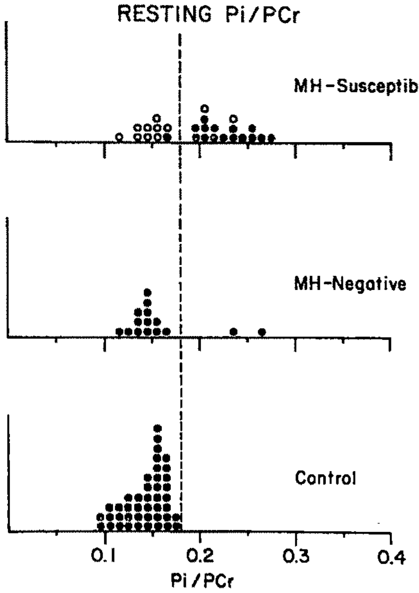


Figure 3. Distributions of resting Pi/PCr values determined by ^{31}P NMR for normal controls and MH-negative and MH-susceptible patients, as diagnosed by halothane/caffeine contracture test results. The *open circles* represent those patients who had an abnormally slow postexercise recovery of PCr/Pi. The *closed circles* represent those subjects who had normal postexercise recovery rates of PCr/Pi For the controls, $n = 43$; for the MH-negative group, $n = 15$; for the MH-susceptible group, $n = 30$. The means are 0.202 ± 0.044 for the MH-susceptible group, 0.157 ± 0.043 for the MH-negative group, and 0.141 ± 0.026 for the control group. The MH-susceptible group is significantly different from each of the other two groups ($P < 0.005$). There is no difference between the MH-negative and control groups. The *dashed line* is the Pi/PCr value used as the lower limit for a positive result. A value of 0.18 or greater was considered to be abnormal.

MH-negative patient are shown in Figure 2. There are similar peaks in both spectra. However, the Pi/PCr ratio is measurably higher in the patient who is MH-susceptible. The distributions of resting Pi/PCr values for MH-susceptible, MH-negative, and control groups are shown in Figure 3. The MH-susceptible group (0.202 ± 0.044) has a significantly ($P < 0.005$) higher Pi/PCr than both the MH-negative (0.152 ± 0.043) and the control group (0.141 ± 0.026). The MH-negative and control groups are not significantly different. There are 10 MH-susceptible patients who had resting Pi/PCr values that overlapped with control values. However, nine of these patients had slower than normal postexercise recovery of PCr/Pi (see below). Two patients who were determined to be MH-negative by contracture testing had elevated Pi/PCr values.

Phosphorus nuclear magnetic resonance spectra obtained during exercise and postexercise recovery from an MH-susceptible patient and an MH-negative patient are shown in Figure 4. As recovery progresses, the PCr peak increases and the Pi peak decreases in size. Plots of PCr/Pi versus time, obtained from the spectra for each of the two patients shown in Figure 4, are shown in Figure 5. The recovery rate of PCr/Pi can be easily determined from the slope of each of these curves. The curve for the MH-susceptible patient has a significantly smaller slope than that for the MH-negative patient, indicating a slower recovery rate of PCr/Pi. In fact, the slope is lower than that observed for any control or MH-negative patient studied (see below). Because the signal-to-noise ratio for Pi decreases as recovery progresses (as demonstrated by the spectra in Figure 4), the most accurate measurements are made early during recovery. For this reason, recovery rates were obtained from the first 2 min of recovery. This resulted in three accurately measured data points (final minute of exercise, first and second minute of recovery) on the curve for determining the slope ($PCr \cdot Pi^{-1} \cdot min^{-1}$). The energy states—characterized by PCr/Pi, percent of PCr depletion from rest, and pH—at the end of exercise for the MH-susceptible and MH-negative groups are shown in Table 4. There is no difference in any of these parameters between the two groups.

The distributions of recovery rates in the MH-susceptible, the MH-negative, and the control groups are shown in Figure 6. The MH-susceptible group (1.50 ± 0.171 $PCr \cdot Pi^{-1} \cdot min^{-1}$) had a significantly ($P < 0.02$) slower recovery rate than either the MH-negative (2.11 ± 1.07 $PCr \cdot Pi^{-1} \cdot min^{-1}$) or the control (2.25 ± 0.828 $PCr \cdot Pi^{-1} \cdot min^{-1}$) group. There is no difference between the MH-negative and control groups. Fifteen MH-susceptible patients had recovery rates that overlapped with normal controls; 11

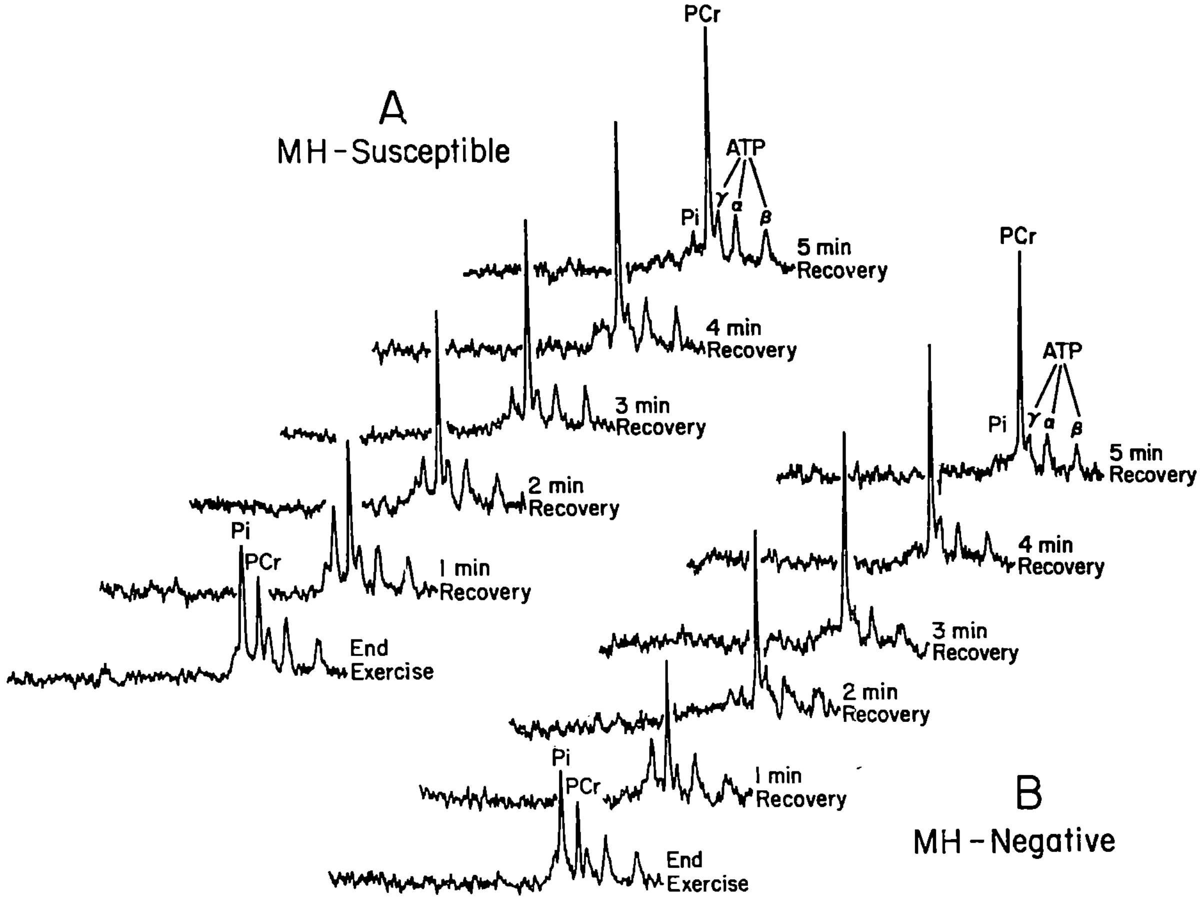


Figure 4. Phosphorus nuclear magnetic resonance spectra of forearm muscles obtained during the final minute of exercise and during postexercise recovery from an MH-susceptible (A) and an MH-negative (B) patient. The Pi peak decreases and the PCr peak increases as recovery ensues. These spectra were used to calculate the ratios of PCr/Pi for each patient to obtain the plots of recovery rate depicted in Figure 5.

had slower recovery rates. However, 14 of the 15 MH-susceptible subjects with recovery rates in the control range had high resting Pi/PCr values. Only one MH-susceptible patient with a "normal" recovery rate also had a "normal" resting Pi/PCr. None of the MH-negative patients had recovery rates slower than normal controls.

Intracellular pH values in the three groups during rest, during the last minute of exercise, and during recovery are shown in Table 5. There is no difference between any of the groups at rest or during exercise or recovery.

Sensitivity and specificity are indices determined in reference to a true diagnosis. Because it is difficult to evaluate the NMR test with reference to a true diagnosis of MH susceptibility in a large enough sample, these values are not easily obtained. For comparing a screening test to a reference test, Buck and Gart suggested three indices of agreement: copositivity, conegativity, and overall agreement (25). Copositivity is defined as the probability that the screening test will be positive when the reference test is positive and is analogous to sensitivity. Conegativity is defined as the probability that the screening test will be negative when the reference test is negative and is analogous to specificity. Overall agreement is the percentage of individuals with identical results in the two tests. These parameters were used to compare the NMR test and the contracture test in diagnosing MH susceptibility.

Receiver operating characteristic curves are plots of sensitivity versus specificity and show the consequences of choosing a particular cutoff. Receiver operating characteristic curves for the NMR test compared with the contracture test are shown in Figures 7 and 8, substituting copositivity for sensitivity and conegativity for specificity. These curves were used to establish cutoff points for the NMR test. Figure 7 shows the ROC curves for the individual resting NMR test and recovery NMR test. The ideal ROC curve would maximize both copositivity and conega-

Table 4. Characterization of the Energy State Before Recovery, at End-Exercise

Group	PCr/Pi at end-exercise[a]	% of rest PCr at end-exercise	pH at end-exercise
MH-susceptible ($n = 26$)	0.619 ± 0.339	37.6 ± 13.8	6.75 ± 0.20
Normal recovery rate ($n = 15$)	0.637 ± 0.264	41.1 ± 10.6	6.80 ± 0.18
Slow recovery rate ($n = 11$)	0.597 ± 0.425	33.3 ± 16.8	6.69 ± 0.23
MH-negative ($n = 14$)	0.503 ± 0.260	31.1 ± 10.6	6.75 ± 0.18

PCr, phosphocreatine; Pi, inorganic phosphate; MH, malignant hyperthermia.
All values are expressed as mean ± SD.
All *P* values are not significant.
[a] These values were determined by peak areas. The PCr/Pi ratios by peak heights were roughly 1 in all groups, as described in Methods.

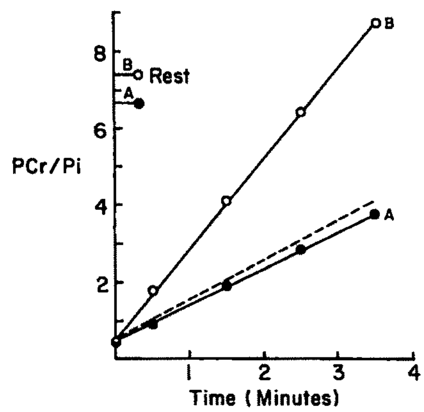


Figure 5. Plots of PCr/Pi versus time for the MH-susceptible (*A*) and MH-negative (*B*) patients whose spectra are shown in Figure 4. The recovery rate of PCr/Pi is determined from the slope of these lines. The *dashed line* represents the slowest recovery rate observed among the control and MH-negative patients studied (1.0 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$). The recovery of PCr/Pi is considerably slower for the MH-susceptible patient (*A*). The slope of curve *A* is 2.4 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$ and of curve *B* 0.9 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$. The overshoot of PCr/Pi above the resting value during recovery in (*B*) is a commonly seen phenomenon and returns to the resting value if recovery is followed long enough.

tivity (i.e., both 100%). The ROC curve for resting Pi/PCr shows that the best cutoff point would be between 0.15 and 0.19, depending on whether one wants to maximize copositivity or conegativity. This agrees with values determined from previous results (7). A cutoff of 0.15 (i.e., a Pi/PCr value ≥ 0.15 is positive) would give a copositivity of 82% and a conegativity of 67%. A cutoff of 0.17–0.19 would give a copositivity of 63% and a conegativity of 87%.

The ROC curve for recovery ($PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$) shows that, because it is concave, this test alone is not a very good diagnostic test. Choosing a cutoff point from this curve is quite difficult because there is no point with both a copositivity and conegativity greater than 60%. A cutoff of 1.0 (i.e., a $PCr{\cdot}Pi^{-1}{\cdot}min^{-1} < 1.0$ is positive) gives the highest overall agreement (66%) and gives a copositivity of 46% and a conegativity of 100%. A cutoff of 1.5 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$ gives a copositivity of 54% and a conegativity of 71%, but an overall agreement of only 55%.

Receiver operating characteristic curves for the combination of resting Pi/PCr and recovery $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$ (i.e., a positive test result is an abnormal Pi/PCr and/or $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$) are shown in Figure 8. From this figure one can determine the best cutoff points to be 1.0 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$ for recovery and 0.17–0.19 for resting Pi/PCr. These cutoff points used in combination (i.e., a positive NMR result being a Pi/PCr ≥0.17–0.19 or a $PCr{\cdot}Pi^{-1}{\cdot}min^{-1} < 1.0$) give a copositivity of 96% and a conegativity of 87% for the NMR test when compared with the contracture test. Figure 9 shows the overall agreement between the combined NMR test (rest plus recovery) and the contracture test at different cutoff points. One can see that the maximum overall agreement (93%) is achieved with cutoffs of <1.0 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$ and ≥0.17–0.19 Pi/PCr.

From Figures 8 and 9 cutoffs for the NMR test were chosen to be 1.0 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$ and 0.18 Pi/PCr (midpoint between 0.17 and 0.19). The combination of these two NMR tests, with MH susceptibility diagnosed by a high resting Pi/PCr (≥0.18) or a slow recovery rate (<1.0 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$), was more accurate than either alone. This combination NMR test revealed one "false-negative" and two "false-positive" patients, when compared with contracture test results. The two false-positive patients had elevated Pi/PCr values of 0.23 and 0.27 with normal recovery rates of 1.60 and 2.81 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$, respectively. The one false-negative patient had a resting Pi/PCr value of 0.161 and a recovery rate of 2.69 $PCr{\cdot}Pi^{-1}{\cdot}min^{-1}$. The three patients who had had documented MH episodes all had elevated resting Pi/PCr values and normal recovery rates.

For the reasons stated above, sensitivity and specificity are not readily determined when comparing two diagnostic tests without knowing a true diagnosis for each patient. Copositivity and conegativity are analogous to, but not identical to, sensitivity and specificity, respectively. However, estimates of sen-

Table 5. Intracellular pH of Muscle Studied at Rest, During Exercise, and During Recovery

Group	Rest pH	End-exercise pH	1-min recovery pH	2-min recovery pH
MH-susceptible (n = 27, 26)[a]	7.13 ± 0.10	6.75 ± 0.20	6.67 ± 0.24	6.60 ± 0.21
MH-negative (n = 15, 14)	7.12 ± 0.12	6.75 ± 0.17	6.70 ± 0.17	6.65 ± 0.17
Control (n ± 43, 35)	7.10 ± 0.01	6.71 ± 0.22	6.66 ± 0.22	6.62 ± 0.26

MH, malignant hyperthermia.

P values for differences among the three groups during rest, exercise, and recovery are not significant.

[a] For the sample sizes (n), the first number is for resting nuclear magnetic resonance data, the second for exercise and recovery data.

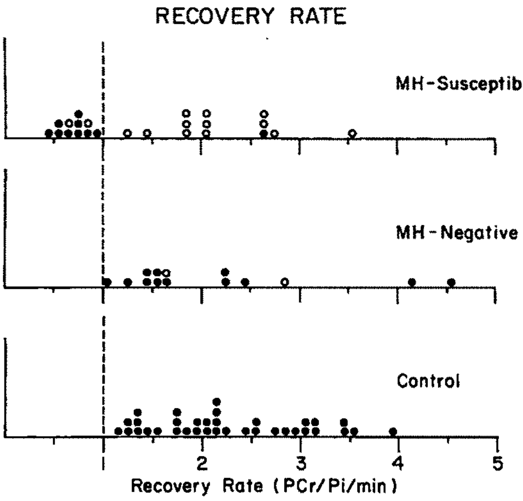


Figure 6. Distributions of recovery rates of PCr/Pi determined by ^{31}P NMR for normal controls and MH-negative and MH-susceptible patients, as diagnosed by halothane/caffeine contracture test results. Recovery rates were calculated from the slopes of the linear relationship of PCr/Pi versus time for the first 2 min of recovery. The *open circles* represent those patients with abnormally high resting Pi/PCr values. The *closed circles* represent those subjects who had normal resting Pi/PCr values. In addition, recovery rates were not obtained for eight controls and four biopsied patients. For the control group, n = 35; for the MH-negative group, n = 14; for the MH-susceptible group, n = 26. The means are 1.50 ± 0.872 $\text{PCr·Pi}^{-1}\text{·min}^{-1}$ for the MH-susceptible group, 2.11 ± 1.07 $\text{PCr·Pi}^{-1}\text{·min}^{-1}$ for the MH-negative group, and 2.25 ± 0.828 $\text{PCr·Pi}^{-1}\text{·min}^{-1}$ for the control group. The MH-susceptible group has a significantly slower recovery rate of PCr/Pi than either the MH-negative or the control group ($P <$ 0.02). The control and MH-negative groups are not significantly different. The *dashed line* is the recovery rate used as the upper limit for a positive result. A recovery rate of less than 1.0 $\text{PCr·Pi}^{-1}\text{·min}^{-1}$ was considered abnormal.

sitivity and specificity can be obtained for the NMR test by comparing it with the contracture test using the methods of Buck and Gart (25,26). Based on clinical experience and preliminary data obtained from contracture testing in pigs, the halothane/caffeine contracture test used in our laboratory has a sensitivity of 95% and a specificity of 95% (27,28). From the results shown in Table 6, a sensitivity of 98.8% ± 11.8% and a specificity of 95.3% ± 20.3% for the NMR test can be calculated.

Discussion

The results reported here confirm those reported in our previous publication (7). Malignant hyperthermia-susceptible patients, in general, had a significantly higher resting Pi/PCr value and a slower post-exercise recovery rate. Phosphorus nuclear magnetic resonance determination of these parameters demonstrated an overall agreement of 93% with the in vitro halothane/caffeine contracture test in diagnosing MH susceptibility. Not all MH-susceptible patients had both a high resting Pi/PCr and a slow recovery rate. However, with the exception of only one patient, those MH-susceptible subjects with normal resting Pi/PCr values all had slow recovery rates. All of the MH-susceptible patients with normal recovery rates, except that one same patient, had a high resting Pi/PCr ratio. All of the MH-negative patients had normal recovery rates, and only two of these patients had elevated resting Pi/PCr values. Therefore, the combination of determining resting Pi/PCr and recovery rate by NMR is quite sensitive (98.8% ± 11.8%) and specific (95.3% ± 20.3%) in diagnosing MH susceptibility in the population studied, when compared with the halothane/caffeine contracture test.

The one false-negative patient (by NMR) had a clearly normal resting Pi/PCr (0.161) and recovery rate (2.59 $\text{PCr·Pi}^{-1}\text{·min}^{-1}$) with a maximum halothane contracture of 1.5 g on in vitro testing. The patient's sister had developed an elevated temperature during anesthesia and subsequently had an equivocal result on in vitro halothane/caffeine contracture testing. Her mother had also had an equivocal result on contracture testing. Histologic examination of the muscle biopsy specimen from this patient revealed nonspecific abnormalities of scattered, small angulated fibers. She had no clinical signs or symptoms of myopathy. It is unclear whether

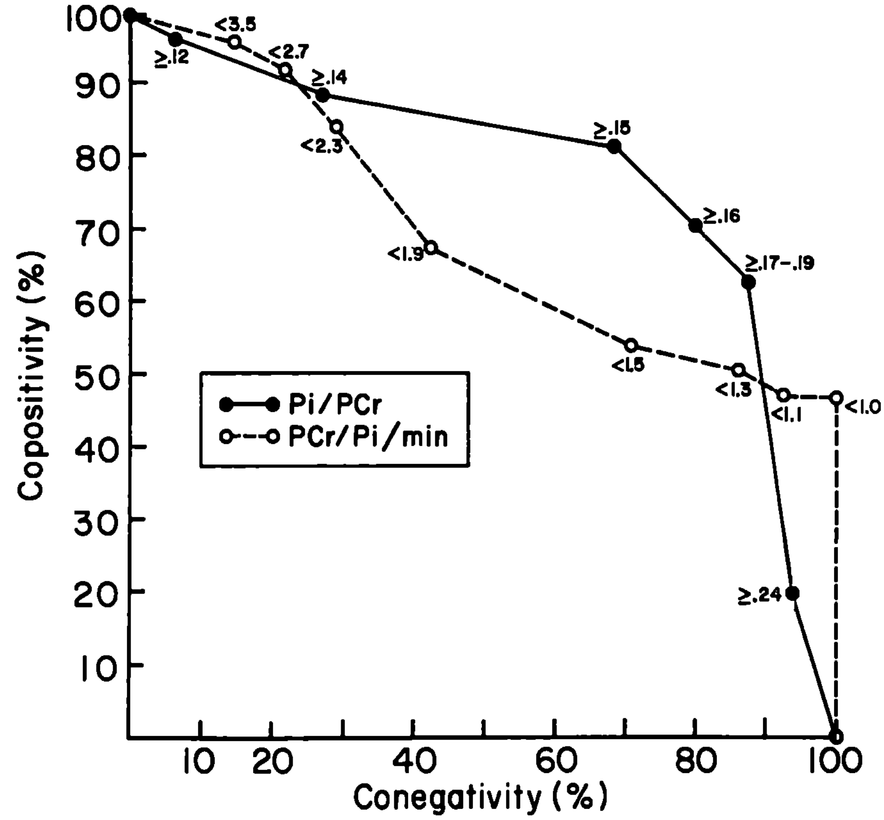


Figure 7. Receiver operating characteristic curves for NMR determination of resting Pi/PCr (●——●) and postexercise recovery of PCr/Pi (○----○), in reference to the contracture test results. The numbers by each data point represent the cutoff point used in determining the copositivity and conegativity for each point.

this represents a false-negative NMR test or a false-positive contracture test result.

The two false-positive patients had normal recovery rates (1.60 and 2.81 PCr·Pi^{-1}·min^{-1}) but had resting Pi/PCr values (0.23 and 0.27) that were clearly well above normal. One of these patients (number 5) was tested a second time by NMR, with no difference in the result. Muscle samples from both patients had a maximum contracture response of 0.3 g to halothane and no response to 2 mM caffeine. Patient 5 had experienced masseter muscle rigidity after exposure to succinylcholine—often found to be an early sign of MH—but had no family history of MH (2). The other patient (number 20) had a brother who developed an elevated temperature during anesthesia and subsequently died. Neither of these patients had relatives who were tested for MH susceptibility. Neither patient had evidence of clinical neuromuscular disease. The histologic studies of the muscle specimens from each of these patients were reviewed; they revealed only nonspecific findings of variation in fiber size, within the limits of the normal. We studied six patients with a history of masseter muscle rigidity. Two of these patients were MH-negative by contracture testing, of which one was patient 5. The other patient had a normal resting Pi/PCr value and recovery rate. The four MH-susceptible patients all had abnormal NMR parameters (three with elevated resting Pi/PCr and one with a slow recovery rate).

Some false-positive NMR results are expected because an elevated resting Pi/PCr and a slow recovery rate have been reported for several muscle diseases and conditions (Table 1). In the general population the expected predictive value would be quite low because the prevalence of MH is relatively low. Therefore, the NMR test may not be useful for mass screening in the general population, because the prevalence of other myopathies is probably greater than that of MH. However, in a population of patients with a family or personal history of MH, as is seen at an MH diagnostic center, the predictive value of NMR testing is expected to be high, as in this study. Moreover, the predictive value should be even higher for a population of patients who are relatives of biopsy-proven MH-susceptible individuals. There does seem to be an association between MH and other myopathies, most notably central core disease and some muscular dystrophies (27,29,30). Because the NMR abnormalities are found in many of these disorders, NMR would not be of use in diagnosing MH susceptibility in patients with neuromuscular symptoms suggesting myopathy. Muscle contracture

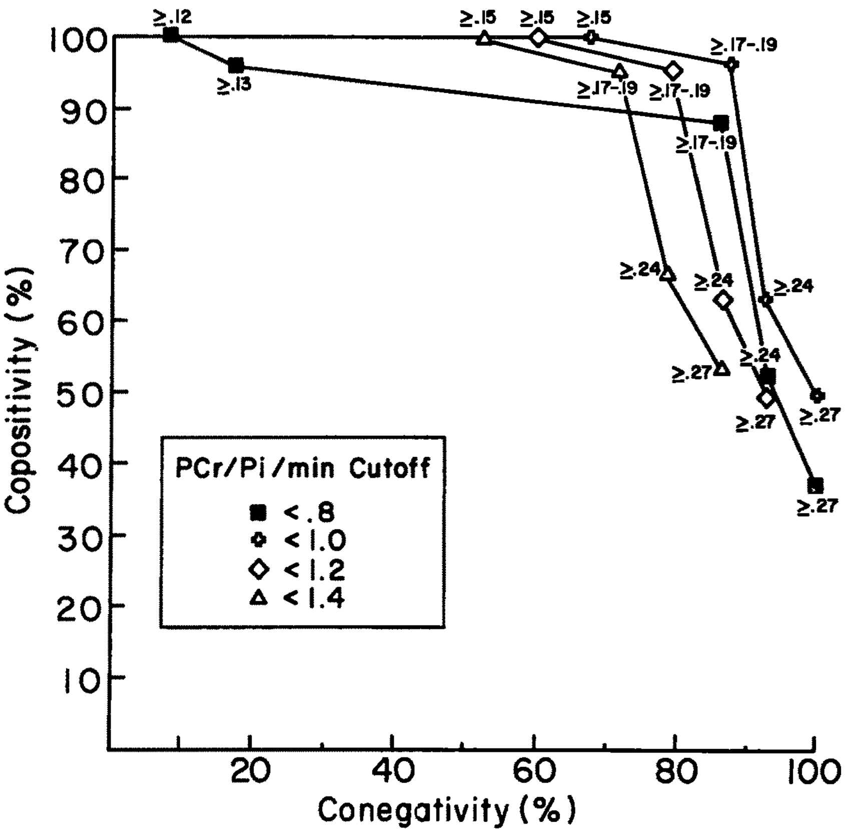


Figure 8. Receiver operating characteristic curves for the combined resting Pi/PCr and recovery PCr·Pi^{-1}·min^{-1} NMR test, in reference to the contracture test results. A positive NMR test result was considered to be either an elevated resting Pi/PCr or a slow recovery PCr·Pi^{-1}·min^{-1}, or both. The numbers by each data point represent the cutoff point for resting Pi/PCr. Each individual curve represents an ROC curve using a particular PCr·Pi^{-1}·min^{-1} cutoff (■, <0.8; ◆, <1.0; ◇, <1.2; △, <1.4) while varying the resting Pi/PCr cutoff point.

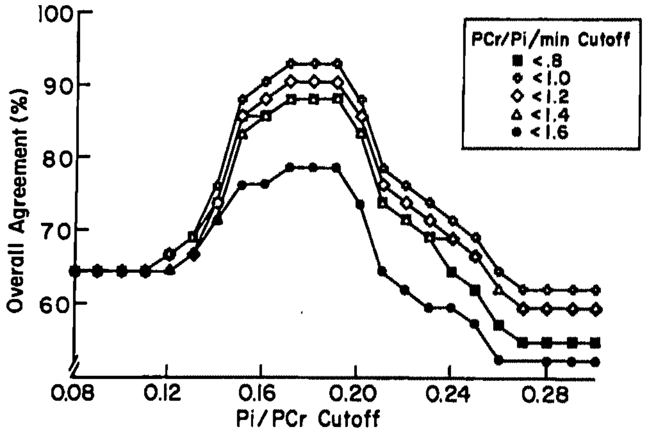


Figure 9. Plot of overall agreement between the contracture test and the combined NMR test (resting Pi/PCr and recovery PCr·Pi^{-1}·min^{-1}) at different cutoff points for the NMR test. Each individual curve represents a different PCr·Pi^{-1}·min^{-1} cutoff point, while varying the Pi/PCr cutoff.

testing would be required to diagnose MH susceptibility in these patients.

The biochemical significance of the Pi/PCr ratio has been detailed in previous publications (21–25,31). It is a measure of the energy state of the tissue, which in muscle is controlled by oxidative phosphorylation. The basis for the observed elevation in resting Pi/PCr and the slow recovery rate of PCr/Pi in MH-susceptible patients has been discussed in previous publications (7). In short, the NMR abnormalities can best be explained by defects in calcium cycling. This hypothesis is also consistent with the current theories of mechanisms of an MH episode.

The MH-susceptible group was quite heterogeneous. Fourteen patients had elevated resting Pi/PCr with normal postexercise recovery of PCr/Pi. Nine patients had slow recovery rates with normal resting Pi/PCr. Two patients had both an elevated resting Pi/PCr and a slow recovery rate. Several of the patients studied here are relatives of one another. We studied four separate families, three of which each had two MH-susceptible members in this study, and one of which had three MH-susceptible members in this study. The specific NMR abnormality was consistent within those families. All of these MH-susceptible patients had elevated resting Pi/PCr values and normal recovery rates. This lends further evidence to the concept that MH represents a spectrum of disease (1,4). This study suggests that there may be at least two populations of MH-susceptible patients (as determined by contracture testing)—those with increased resting Pi/PCr and those with slow postexercise recovery. Perhaps each of these

Table 6. Fourfold Tables Comparing the Nuclear Magnetic Resonance Tests With the Contracture Test

	NMR test result[a]								
	Rest Pi/PCr			Recovery rate			Rest Pi/PCr or recovery rate		
	Elevated	Normal	Total	Slow	Normal	Total	Abnormal	Normal	Total
Contracture test result									
+	17	10	27	11	13	24	26	1	27
−	2	13	15	0	14	14	2	13	15
Total	19	23	42	11	27	38	28	14	42
Overall agreement			71.4%			65.8%			92.9%
Copositivity			56.7%			45.8%			96.3%
Conegativity			86.7%			100%			86.7%

NMR, nuclear magnetic resonance; Pi, inorganic phosphate; PCr, phosphocreatine.

[a] A positive test is considered to be a resting Pi/PCr $\geq$0.18 or a recovery rate $\leq$1.0 PCr·Pi^{-1}·min^{-1}.

groups has different defects in calcium cycling. This could help to explain some of the discrepancies in the literature concerning calcium handling in muscle from unchallenged MH-susceptible humans and swine (4).

Although the specificity of the NMR test may be as low as 75% (95.3% ± 20.3%) in this study, sources of false positives (i.e., other muscle disorders) can be greatly decreased by limiting the test population to those individuals who have a biopsy-proven MH-susceptible relative. In our study the two false-positive patients (by NMR) had no relatives that underwent biopsy or other MH testing. A sensitivity of 98.8% ± 11.8% is as good as that estimated for the contracture test. However, there is not much separation between the MH-susceptible population and the normal population (Figures 3 and 6). Dantrolene has been shown to decrease intracellular calcium in muscle of MH-susceptible patients not exposed to anesthesia (32). We have previously shown in one MH-susceptible patient that dantrolene can normalize the elevated resting Pi/PCr (7). Although neither of these studies had controls, perhaps dantrolene depression of resting Pi/PCr could be of help in diagnosing MH-susceptible patients by ^{31}P NMR. Two recent reports suggest that determination of intracellular pH by NMR during exercise and recovery may be helpful in diagnosing MH susceptibility (33,34). Although our protocols differed, pH differences were not found in this study or in the previously reported one (7).

In this blinded study, we have demonstrated that ^{31}P NMR spectroscopy may be an accurate noninvasive means of diagnosing MH susceptibility. The major advantage of the NMR test over the contracture test is that it is noninvasive, eliminating the risks, inconvenience, and discomfort of the present biopsy test. The test can be accomplished in less than 1 h and can be easily repeated. Moreover, because it is noninvasive, it is an ideal tool for studying extended families to achieve a better definition of the inheritance pattern of this disease. However, because equipment, protocols, and methods of analysis may differ among various NMR laboratories, normal values and limits of abnormality need to be determined for each laboratory.

Patients who are MH-susceptible have a higher resting Pi/PCr and/or slower postexercise recovery rate of PCr/Pi when compared to MH-negative and normal controls. By measuring these parameters with ^{31}P NMR spectroscopy, MH-susceptible individuals can be distinguished from nonsusceptible individuals noninvasively. With a sensitivity of 98.8% ± 11.8% and a specificity of 95.3% ± 20.3%, the NMR test for MH susceptibility may be as accurate as the contracture test. The ^{31}P NMR test appears to be a promising new noninvasive technique for determining MH susceptibility.

The authors express their sincere thanks to Ed Pequignot for his advice concerning statistical treatment of the data. They also thank Dr. Jeffrey E. Fletcher for his advice.

References

1. Gronert GA. Malignant hyperthermia. Anesthesiology 1980; 53:395–423.
2. Rosenberg H. Clinical presentation of malignant hyperthermia. Br J Anaesth 1988;60:268–73.
3. Heffron JJA. Malignant hyperthermia: biochemical aspects of the acute episode. Br J Anaesth 1988;60:274–8.
4. Ellis FR, Heffron JJA. Clinical and biochemical aspects of malignant hyperpyrexia. Rec Adv Anaesth Analg 1985;15:173–207.
5. Ranklev E, Henriksson KG, Fletcher R, Germundsson K,

Oldfors A, Kalimo H. Clinical findings and muscle biopsy findings in malignant hyperthermia susceptibility. Acta Neurol Scand 1986;74:452–9.

6. Ording H. Diagnosis of susceptibility to malignant hyperthermia in man. Br J Anaesth 1988;60:287–302.
7. Olgin J, Argov Z, Rosenberg H, Tuchler M, Chance B. Noninvasive evaluation of malignant hyperthermia susceptibility with phosphorus nuclear magnetic resonance spectroscopy. Anesthesiology 1988;68:507–13.
8. Argov Z, Bank WJ, Maris J, Peterson P, Chance B. Bioenergetic heterogeneity of human mitochondrial myopathies as demonstrated by in vivo phosphorus magnetic resonance spectroscopy. Neurology 1987;37:257–62.
9. Argov Z, Bank WJ, Maris J, Chance B. Muscle energy metabolism in McArdle's syndrome by in vivo phosphorus magnetic resonance spectroscopy. Neurology 1987;37:1720–4.
10. Bank WJ, Argov Z, Leigh JS, Chance B. The value of ^{31}P NMR in the diagnosis and monitoring the course of human myopathies. Ann NY Acad Sci 1987;508:448–50.
11. Younkin DP, Berman P, Sladky J, Bank WJ, Chance B. ^{31}P NMR studies in duchene muscular dystrophy: age related metabolic changes. Neurology 1987;37:165–9.
12. Edwards RHT, Wilkie DR, Dawson MJ, Gordon RE, Shaw D. Clinical use of nuclear magnetic resonance in the investigation of myopathy. Lancet 1982;i:725–31.
13. Argov Z, Renshaw P, Bank WJ. Abnormal oxidative metabolism of hypothyroid muscle: in vivo ^{31}P NMR of humans and rats (abstract). Neurology 1987;36(Suppl 1):138.
14. Zochonde DW, Thompson TR, Driedger AA, Bolton CF, Strong MJ, Hudson AJ. Topical ^{31}P NMR spectroscopy in human forearm denervation (abstract). Neurology 1987; 36(Suppl 1):138.
15. McCully KK, Argov Z, Boden B, Brown R, Bank WJ, Chance B. Detection of muscle injury in humans with ^{31}P magnetic resonance spectroscopy. Muscle Nerve 1987;1:62–6.
16. Chan L. The current status of magnetic resonance spectroscopy—basic and clinical aspects. West J Med 1985;143:773–81.
17. Radda GK. The use of NMR spectroscopy for the understanding of disease. Science 1986;233:640–5.
18. Fletcher JE, Rosenberg H. In vitro interaction between halothane and succinylcholine in human skeletal muscle: implications for malignant hyperthermia and masseter muscle rigidity. Anesthesiology 1985;63:190–4.
19. Britt BA. Muscle assessment in MH-susceptible patients. In: Britt BA, ed. Malignant hyperthermia. Boston: Martinus Nijhoff, 1987:193–268.
20. Larach MG, for the North American Malignant Hyperthermia Group. Standardization of the caffeine halothane muscle contracture test. Anesth Analg 1989;69:511–5.
21. Chance B, Eleff S, Leigh JS, Sokolow D, Sapega A. Mitochondrial regulation of phosphocreatine/inorganic phosphate ratios in exercising human muscle: a gated ^{31}P NMR study. Proc Natl Acad Sci USA 1981;78:6714–8.
22. Chance B, Clark BJ, Nioka S, et al. Phosphorus nuclear magnetic resonance spectroscopy in vivo. Circulation 1985;72: IV103–10.
23. Chance B, Leigh JS, Clark BJ, et al. Control of oxidative metabolism and oxygen delivery in human skeletal muscle: a steady-state analysis of work/energy cost transfer function. Proc Natl Acad Sci USA 1985;82:8384–8.
24. Taylor DJ, Bore PJ, Styles P, Gadian DG, Radda GK. Bioenergetics of intact human muscle: a ^{31}P nuclear magnetic resonance study. Mol Biol Med 1983;1:77–94.
25. Buck AA, Gart JJ. Comparison of a screening test and a reference test in epidemiologic studies. I. Indices of agreement and their relation to prevalence. Am J Epidemiol 1966;83:586–92.
26. Gart JJ, Buck AA. Comparison of a screening test and a reference test in epidemiologic studies. II. A probabilistic model for comparison of diagnostic tests. Am J Epidemiol 1966;83:593–602.
27. Heiman-Patterson T, Fletcher JE, Rosenberg H, Tamoush AJ. Halothane caffeine contracture testing in neuromuscular disease. Muscle Nerve 1988;11:453–8.
28. Allen G, Rosenberg H. Caffeine and halothane contracture testing in swine using the recommendations of the North American Malignant Hyperthermia Group. Anesthesiology 1990;72:71–6.
29. Brownell AKW. Malignant hyperthermia: relationship to other diseases. Br J Anaesth 1988:60:303–8.
30. Heiman-Patterson T, Natter HM, Rosenberg HR, Fletcher JE, Tamoush AJ. Malignant hyperthermia susceptibility in X-linked muscle dystrophies. Pediatr Neurol 1986;2:356–8.
31. Chance B. ^{31}P NMR in clinical biochemistry: evaluation of muscle performance. Ann NY Acad Sci 1984;428:318–32.
32. Lopez JR, Medina P, Alamo L. Dantrolene sodium is able to reduce the resting ionic $[Ca^{2+}]i$ in muscle from humans with malignant hyperthermia. Muscle Nerve 1987;10:77–9.
33. Laschuk MJ, Lee RJ, Zochonde DW, Driedger AL, Gordon Thompson T. ^{31}P NMR measured exercise-induced skeletal muscle acidosis in MHS individuals (abstract). Can J Anaesthesia 1987;34:S65–6.
34. Kozak-Reiss G, Gascard JP, Herve P, Jehenson P, Syrota A. Malignant and exercise hyperthermia: investigation of 73 subjects by contracture tests and ^{31}P NMR spectroscopy (abstract). Anesthesiology 1988;69:A415.

Cerebral Blood Flow Autoregulation Is Preserved During Cardiopulmonary Bypass in Isoflurane-Anesthetized Patients

L. John Aladj, MD, Narda Croughwell, CRNA, L. R. Smith, PhD, and J. G. Reves, MD

ALADJ LJ, CROUGHWELL N, SMITH LR, REVES JG. Cerebral blood flow autoregulation is preserved during cardiopulmonary bypass in isoflurane-anesthetized patients. Anesth Analg 1991;72:48–52.

In 21 patients undergoing elective coronary artery bypass surgery, cerebral blood flow (CBF) was measured during hypothermic nonpulsatile cardiopulmonary bypass to test the hypothesis that isoflurane abolished the mean arterial pressure-CBF relation (pressure-flow autoregulation). Cerebral blood flow was determined by ^{133}Xe clearance. The patients were randomly divided into three groups according to anesthesia during cardiopulmonary bypass: group 1 received midazolam and fentanyl; group 2 received, in addition to midazolam and fentanyl, 0.6% isoflurane; and group 3 received, in addition to midazolam and fentanyl, 1.2% isoflurane. The groups were maintained at a constant temperature, Pa_{O_2}, Pa_{CO_2}, and pump flow during CBF measurements. Mean arterial pressure was increased by phenylephrine ≥25% after the first CBF determination. Isoflurane decreased mean arterial pressure significantly ($P < 0.05$) and was associated with lower CBF. Increasing the mean arterial pressure 29% in group 1, 25% in group 2, and 34% in group 3 had no effect on CBF. We conclude that, within the range studied, pressure-flow CBF autoregulation is preserved during isoflurane anesthesia administered for cardiopulmonary bypass.

Key Words: BRAIN, BLOOD FLOW—during cardiopulmonary bypass. ANESTHESIA, CARDIOVASCULAR—cerebral blood flow and cardiopulmonary bypass. ANESTHETICS, VOLATILE—isoflurane.

In a recent clinical study isoflurane administered during cardiopulmonary bypass (CPB) reduced cerebral metabolic oxygen consumption (CMR_{O_2}) more than fentanyl did; however, the fact that cerebral blood flow (CBF) was not significantly lower in patients receiving isoflurane suggested a loss of metabolic autoregulation (1). The loss of metabolic autoregulation may suggest, in turn, loss of pressure-flow autoregulation such that CBF becomes dependent on cerebral perfusion pressure. The purpose of this investigation was to do a systematic study of pressure-flow cerebral autoregulation during hypothermic CPB with isoflurane. The hypothesis was that isoflurane would disrupt pressure-flow autoregulation, that is, that CBF would be perfusion pressure-dependent during CPB in patients anesthetized with isoflurane.

Methods

After institutional approval and informed consent, 21 patients undergoing elective cardiac surgery and hypothermic CPB were studied. Patients with known cerebrovascular disease, history of transient cerebral ischemia, carotid bruits, seizure history, or uncontrolled hypertension (defined as diastolic blood pressure >90 mm Hg) were excluded from the study. Two different concentrations of isoflurane were administered during nonpulsatile CPB and a third group served as control. Patients were allocated to one of three groups from a random number table. Group 1 ($n = 7$) served as a control group: it received no isoflurane but received the same basal anesthetic as the two isoflurane groups (midazolam and fentanyl); group 2 ($n = 7$) received 0.6% isoflurane; and group 3 ($n = 7$) received 1.2% isoflurane. There was no attempt to equalize the perfusion pressure between groups with the administration of phenylephrine or a change in pump flow.

All patients received 0.1 mg/kg diazepam orally and 0.1 mg/kg morphine sulfate intramuscularly 60–90 min before induction of anesthesia. Before induction all patients underwent placement of a

---

Received from the Heart Center of Duke University Hospital, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina. Accepted for publication August 13, 1990.

Address correspondence to Dr. Reves, Box 3094, Duke University Medical Center, Durham, NC 27710.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

large-bore peripheral intravenous catheter, a pulmonary artery catheter via the right internal jugular vein, and a radial arterial catheter. Anesthesia was induced and maintained with midazolam and fentanyl followed by vecuronium for tracheal intubation. To maintain constant blood levels of the intravenous anesthetic drugs during CBF determinations, fentanyl and midazolam were administered by a pharmacokinetic model-driven drug infusion system (2,3). Use of computer-assisted continuous infusion has been shown to maintain relatively constant plasma levels of drug during CPB. Fentanyl and midazolam plasma levels were set at 2 and 50 ng/mL, respectively, at the time of CBF determinations. Isoflurane was administered at the onset of CPB by a calibrated Fortec (Airco, Inc.) vaporizer in the fresh gas circuit of the pump oxygenator.

Cerebral blood flow determinations were made twice during hypothermia (nasopharyngeal temperature 27°C) with nonpulsatile pump flow of 1.6 $L\cdot min^{-1}\cdot m^{-2}$, first after achieving a stable temperature of 27°C (condition A), and again when residual radioactivity had returned to baseline values (approximately 15 min after the first injection). The latter CBF measurement (condition B) was made after the mean arterial pressure (MAP) was increased ≥25% by the bolus administration of phenylephrine. Phenylephrine was given in 100-μg increments and repeated in 2 min if the target increase was not achieved. Both CBF measurements were made at $Paco_2$ values ranging between 35 and 40 mm Hg (uncorrected for body temperature) and at Pao_2 of 150–250 mm Hg. Cerebral blood flow was determined using ^{133}Xe clearance (4–7). Xenon 133 (1.5 mCi dissolved in 3 mL sterile saline) was injected into the arterial line of the pump oxygenator. The average CBF was calculated from two 16-mm cadmium telluride detectors (with wide angle collimators), which were placed over the right and left temporal lobes. Cerebral blood flow was calculated with modification of the initial slope index technique (4) using the following formula:

$$\text{CBF (mL/100 g}\cdot\text{min)} = -\text{slope}\cdot\lambda\cdot 100,$$

where slope is the slope of the natural logarithm of the count rate of 1-min duration during the first 2 min of the ^{133}Xe washout curve obtained by linear regression and λ is the temperature and hematocrit corrected blood-brain partition coefficient (8).

All variables are presented as mean ± SD. Intergroup comparisons of all nonparametric variables were made using the Wilcoxon rank-sum test. Analysis of variance was used to detect difference in continuous variables. The group effect on the change in CBF between the experimental conditions was analyzed using backward stepwise linear regression. The change in CBF was the dependent variable with group change in MAP, change in Po_2, and change in Pco_2 as the predictor variables.

Table 1. Demographic Variables

	Group 1 (n = 7)	Group 2 (n = 7)	Group 3 (n = 7)
Age (yr)	61 ± 8	55 ± 12	61 ± 8
Procedure			
CABG	5	6	7
MVR/AVR	2	1	—
Duration of CPB (min)	118 ± 41	100 ± 28	112 ± 35
Duration of aortic cross-clamp (min)	64 ± 29	48 ± 24	61 ± 21

CABG, coronary artery bypass grafting; MVR, mitral valve replacement; AVR, aortic valve replacement; CPB, cardiopulmonary bypass.
All values except that for procedure are expressed as mean ± SD.
There were no significant differences between groups.

Results

Twenty-one patients were studied, seven in each of three groups. Randomization produced similar groups: there were no significant differences in baseline demographic characteristics (age, duration of CPB, and duration of aortic cross-clamp) of the three groups (Table 1). Mean arterial pressure, CBF, $Paco_2$, Pao_2, nasopharyngeal temperature, and hematocrit values are listed in Table 2: there were no significant differences with regard to these variables within groups. Decreases in MAP and CBF were predictably greater in the two isoflurane groups than in the control group.

Figure 1 presents MAP and CBF data during the first (condition A) and second (condition B) CBF measurement in groups. Mean arterial pressure is, as mentioned, significantly higher in the control group. In all groups, however, as per protocol, the MAP was increased similarly from condition A to B; 29% in group 1, 25% in group 2, and 34% in group 3. Pressure-flow autoregulation, defined as maintenance of a constant CBF at a sustained, increased (≥25%) MAP, is preserved in each patient. Figure 2 represents the CBF in each patient at the lower and increased MAP conditions. Within each group there was no consistent effect on CBF while MAP was elevated between conditions A and B.

Discussion

The brain, like certain other organs, preserves blood flow and tissue oxygenation by autoregulatory mech-

Table 2. Physiologic Variables

	MAP^A (mm Hg)	MAP^B (mm Hg)	CBF^A (mL·100 g^{-1}·min^{-1})	CBF^B (mL·100 g^{-1}·min^{-1})	Pco$_2^A$ (mm Hg)	Pco$_2^B$ (mm Hg)	Po$_2^A$ (mm Hg)	Po$_2^B$ (mm Hg)	NPT^A (°C)	NPT^B (°C)	Hct (%)
Group 1											
1	41	61	33.7	31.9	35.0	37.0	208	186	27.6	27.6	16
2	62	82	18.1	19.4	39.0	39.0	192	205	27.5	26.5	28
3	83	108	24.8	29.9	36.0	35.0	214	143	27.1	27.4	17
4	38	46	21.8	26.4	37.0	35.0	340	140	28.0	28.0	17
5	67	80	15.2	17.1	37.0	37.0	151	100	28.0	28.0	24
6	70	90	26.8	23.7	36.0	35.0	143	143	27.7	27.6	21
7	74	94	19.9	22.7	35.0	35.0	204	184	27.0	26.6	20
Mean	62[a]	80[a]	22.9[b]	24.5[a]	36.0	35.0	207	158	27.6	27.4	20
SD	16	21	6.2	5.3	1.4	1.4	64	36	0.4	0.6	4
Group 2											
1	25	31	19.8	15.9	38.0	35.0	287	260	26.0	26.7	16
2	26	30	13.1	15.9	40.0	40.0	254	178	28.0	27.0	22
3	35	45	18.9	15.8	36.0	37.0	189	138	26.1	26.1	21
4	46	58	4.5	5.3	37.0	39.0	142	229	28.0	28.0	22
5	22	32	5.4	5.4	41.0	38.0	224	195	28.5	27.0	24
6	45	58	11.6	19.0	40.0	39.0	137	142	27.0	27.0	18
7	25	30	22.1	14.6	37.0	40.0	258	159	27.3	27.6	20
Mean	32	41	13.6	13.2	39.0	40.0	258	159	27.3	27.6	20
SD	10	13	7.0	3.5	1.9	1.6	59	45	0.9	0.6	3
Group 3											
1	34	42	12.1	11.9	35.0	35.0	221	143	27.9	27.6	28
2	23	33	22.1	22.1	38.0	38.0	142	223	27.0	27.0	17
3	50	71	14.5	13.1	36.0	35.0	233	124	27.0	27.0	23
4	31	38	11.7	12.4	32.0	34.0	215	208	26.3	26.9	21
5	36	46	16.5	19.3	37.0	37.0	192	152	27.8	27.7	23
6	27	39	15.7	20.9	36.0	39.0	202	178	24.4	24.8	17
7	44	62	12.5	10.0	39.0	37.0	186	145	28.5	28.0	25
Mean	35	47	15.0	15.7	36.0	35.0	199	175	26.9	27.0	22
SD	9	14	3.6	4.9	2.3	1.6	30	31	1.3	1.0	4

MAP, mean arterial pressure; CBF, cerebral blood flow; Pco$_2$, carbon dioxide tension; Po$_2$, oxygen tension; NPT, nasopharyngeal temperature; Hct, hematocrit; A, before elevation of MAP; B, after elevation of MAP.

All measurements at cardiopulmonary bypass flow of 1.62 L·min^{-1}·m^{-2}.

[a] $P < 0.01$ compared with groups 2 and 3.

[b] $P < 0.05$ compared with groups 2 and 3.

anisms. Cerebral blood flow autoregulation can be viewed in terms of either pressure-flow or metabolism-flow relationships. Pressure-flow refers to the ability of the cerebral vascular bed to alter its resistance in response to a change in pressure and thus maintain a constant flow. Metabolism-flow control of CBF refers to the close association of the level of oxidative metabolism in the brain and the CBF. As oxidative metabolism increases, cerebral vasodilation occurs, thereby increasing CBF. Earlier evidence indicated that the coupling of CMRo$_2$ and CBF was lost when isoflurane was given during CPB (1). This finding, as well as the considerable literature (see below) exploring the metabolic and perfusion pressure relationships with isoflurane, prompted our study of the perfusion pressure-CBF relationship during CPB.

There is an interesting dichotomy of isoflurane

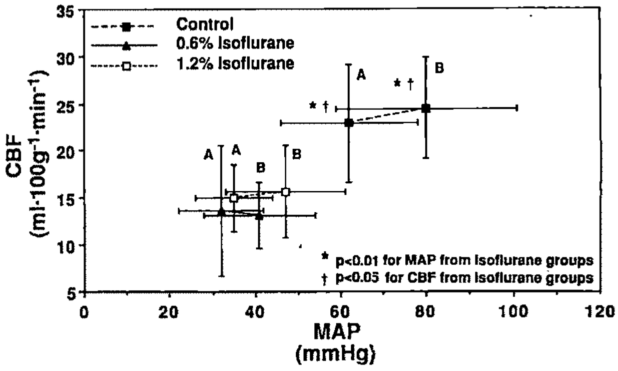


Figure 1. Means and standard deviations of MAP and CBF for patients given midazolam and fentanyl (control) and for patients given either of two doses of isoflurane (0.6% and 1.2%) in addition to midazolam and fentanyl. All measurements were made at hypothermia and during nonpulsatile CPB. Condition A represents the first measurement and B the second, after raising the perfusion pressure ≥20%. Note that CBF is not affected by change in MAP.

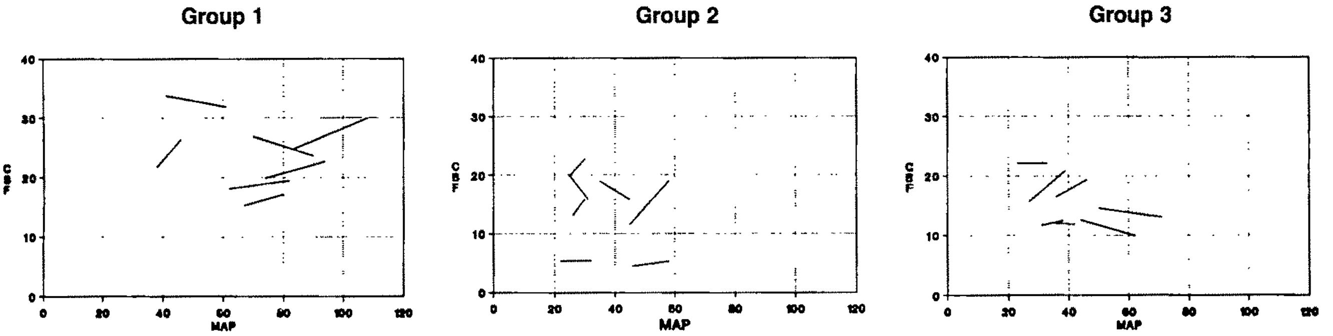


Figure 2. Individual patient CBF and MAP at two different perfusion pressures during normothermic, nonpulsatile CPB. Group 1 is the control (midazolam and fentanyl); group 2 received 0.6% isoflurane in addition; and group 3 received 1.2% isoflurane in addition. Note that there is no pattern in CBF response to change in MAP in the three groups.

action in anesthetized subjects on the usual relationships of CBF to CMRO_2 and MAP. These relationships have been studied using different models and varying species (9–14). Most studies show preservation of pressure-flow but uncoupling of the CMRO_2 to CBF relationships with isoflurane. In a cat model with angiotensin infusion to elevate MAP it was shown that 1.0 MAC isoflurane at normothermia preserved pressure-flow autoregulation (9). In the same experiments CMRO_2 decreased, but CBF remained unchanged, while the dose of isoflurane was increased. Perfusion pressure, increased by phenylephrine infusion, had no effect on CBF at 1.4% isoflurane, showing the preservation of pressure-flow autoregulation at this concentration of isoflurane. It has also been shown that pressure-flow cerebral autoregulation was preserved in dogs receiving 1.4% isoflurane but was lost (became perfusion pressure-dependent) at 2.8% isoflurane (11). In the same studies these investigators demonstrated an uncoupling of CBF and CMRO_2: CBF increased while CMRO_2 decreased as the concentration of isoflurane was increased from 1.4% to 2.8%. A similar association of CBF and CMRO_2 was seen in dogs anesthetized with isoflurane (10). In the study there was an isoflurane dose-effect on CMRO_2 between 1.4% and 3% isoflurane (significant decrease) but no change in CBF.

Clinical studies, although not as well controlled nor as complete as the animal investigations, are in agreement with the laboratory reports. Three studies have described the effect of isoflurane on CBF and CMRO_2 in metabolism in humans undergoing neurosurgical procedures. It has been shown that 0.65 MAC of isoflurane did not change CBF but did decrease CMRO_2 from control (12). In another study a significant decrease in CMRO_2 was found with no change in CBF as the inspired concentration of isoflurane was increased from 0.75% to 1.5% (13). Finally, the effect of isoflurane-induced hypotension on CBF in patients undergoing clipping of cerebral aneurysms revealed that as MAP was reduced from 78 to 51 mm Hg, and then returned to 82 mm Hg, CBF remained unchanged (14). How isoflurane may disrupt metabolism-flow relationships but preserve pressure-flow relationships in normal animals and humans is unclear.

The preservation of pressure-flow autoregulation in subjects anesthetized with isoflurane while not on CPB is consistent with our observations during CPB. During hypothermic nonpulsatile CPB, we examined the effect of isoflurane at two clinically relevant doses on the relationship of CBF and MAP. The data demonstrate that CBF is independent of MAP at 0.6% and 1.2% isoflurane. There was no consistent change in patients when MAP was increased ≥25% during hypothermic CPB. Because the studies were conducted at the lower end of the CBF autoregulation range, had isoflurane obliterated autoregulation a linear relationship of CBF to MAP would have been found. Therefore, we conclude from the data obtained at perfusion pressures of 30–40 mm Hg that pressure-flow autoregulation during hypothermic CPB is maintained when isoflurane is used in doses of 0.6% and 1.2%. This finding is consistent with the animal and clinical data cited above (11–14).

Some comments concerning the experimental approach should be made. Several studies have described variables influencing CBF and autoregulation during CPB. We previously (5) demonstrated that the two factors that significantly affected CBF during CPB were nasopharyngeal temperature and carbon dioxide tension (PCO_2). In our study in the individual patient these variables were kept constant. Isoflurane partial pressures were not measured before CBF determinations; however, others (15) have previously shown that there is rapid equilibration of anesthetic partial pressure between gas delivered via the pump oxygenator and blood (90% within 16 min). The mean time from initiating isoflurane to the first CBF measurement in our study was 36 min. Acid-base management affects autoregulation during hypothermic CPB primarily because of the marked effect of Pco_2 on CBF (6,7). Pressure-flow autoregulation is lost with pH-stat CO_2 management, which results in a relative hypercarbia; therefore, in our present study α-stat blood gas management was employed to preserve autoregulation.

Our study has clinical relevance, but the data apply only to patients managed with α-stat blood gas strategy and to patients without symptoms or history of hypertension and neurovascular disease. The main implication of our data has to do with anesthesia administration during CPB. We have previously reported that isoflurane in a dose-related fashion attenuates the stress response to CPB (16). Because perfusion pressure often decreases during CPB, it is important to know whether pressure-flow autoregulation is preserved with isoflurane. Several groups (5–7,17) have reported intact CBF autoregulation during fentanyl anesthesia. As mentioned before (1), the cerebral hemodynamic and metabolic effects of isoflurane during hypothermic and normothermic CPB have been studied, and it was found that metabolic autoregulation was disrupted during CPB with isoflurane, which is consistent with the animal and non-CPB data in humans (9–14). We found that changing MAP during isoflurane anesthesia does not alter CBF over the ranges commonly encountered during hypothermic CPB. This new knowledge that pressure-flow autoregulation is maintained when isoflurane is used during CPB is reassuring because isoflurane is a useful adjunct to opioid anesthesia during CPB.

References

1. Woodcock TE, Murkin JM, Farrar JK, Tweed WA, Guiraudon GM, McKenziz FN. Pharmacologic EEG suppression during cardiopulmonary bypass: cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and normothermia. Anesthesiology 1987;67:218–24.
2. Reves JG, Glass P, Jacobs JR. Alfentanil and midazolam: new anesthetic drugs for continuous infusion and an automated method of administration. Mt Sinai J Med 1989;56:99–107.
3. Glass PSA, Jacobs JR, Smith LR, et al. Pharmacokinetic model-driven infusion of fentanyl: assessment of accuracy. Anesthesiology (in press).
4. Olesen J, Paulson OB, Lassen NA. Regional cerebral blood flow in man determined by the initial slope of the clearance of intraarterially injected Xe 133. Stroke 1971;2:519.
5. Govier AV, Reves JG, McKay RD. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. Ann Thorac Surg 1984;38:592–600.
6. Prough DS, Stump DA, Roy RC. Response of cerebral blood flow to changes in carbon dioxide tension during hypothermic cardiopulmonary bypass. Anesthesiology 1986;64:576–81.
7. Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of $Paco_2$. Anesth Analg 1987;66:825–32.
8. Chen RYZ, Fan FC, Kim S, Jan KM, Usami S, Chien S. Tissue-blood partition coefficient for xenon: temperature and hematocrit dependence. J Appl Physiol 1980;49:178.
9. Todd MM, Drummond JC. A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. Anesthesiology 1984;60:276–82.
10. Newberg LA, Milde JH, Michenfelder JD. The cerebral metabolic effects of isoflurane at and above concentrations that suppress cortical electrical activity. Anesthesiology 1983;59:23–8.
11. McPherson RW, Traystman RV. Effects of isoflurane on cerebral autoregulation in dogs. Anesthesiology 1988;69:493–9.
12. Algotsson L, Messeter K, Nordstom CH, Ryding E. Cerebral blood flow and oxygen consumption during isoflurane and halothane anaesthesia in man. Acta Anaesthesiol Scand 1988;32:15–20.
13. Madsen JB, Cold GE, Hansen ES, Bardrum B. The effect of isoflurane on cerebral blood flow and metabolism in humans during craniotomy for small supratentorial cerebral tumors. Anesthesiology 1987;66:332–6.
14. Newman B, Gelb AW, Lam AM. The effect of isoflurane-induced hypotension on cerebral blood flow and cerebral metabolic rate for oxygen in humans. Anesthesiology 1986;64:307–10.
15. Nussmeier NA, Moskowite GV, Weiskope RB, Cohen NH, Fisher DM, Eger EI II. In vitro anesthetic washin and washout via bubble oxygenators: influence of anesthetic solubility and rates of carrier gas inflow and pump blood flow. Anesth Analg 1988;67:982–7.
16. Flezzani P, Croughwell ND, McIntyre RW, Reves JG. Isoflurane decreases the cortisol response to cardiopulmonary bypass. Anesth Analg 1986;65:1117–22.
17. Brusino FG, Reves JG, Smith LR, Prough DS, Stump DA, McIntyre RW. The effect of age on cerebral blood flow during hypothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg 1989;97:541–7.

Epidural Morphine With Butorphanol for Postoperative Analgesia After Cesarean Delivery

C. D. Lawhorn, MD, J. D. McNitt, MD, E. E. Fibuch, MD, J. T. Joyce, MD,
and R. J. Leadley, Jr, MBE

LAWHORN CD, McNITT JD, FIBUCH EE, JOYCE JT, LEADLEY RJ Jr. Epidural morphine with butorphanol for postoperative analgesia after cesarean delivery. Anesth Analg 1991;72:53–7

Epidural morphine has been used more and more to provide long-lasting postoperative analgesia after cesarean delivery. However, the incidence of pruritus (20%–93%) and nausea (17%–60%) detract from the usefulness of epidural morphine. The purpose of this study was to evaluate, in 30 patients having epidural anesthesia for cesarean delivery, the analgesic efficacy and side effects when a combination of epidural morphine, a μ-receptor agonist, and butorphanol, a μ-receptor antagonist and κ-receptor agonist, was administered. After clamping of the umbilical cord, patients received 4 mg epidural morphine with 3 mL of normal saline (group 1), 4 mg epidural morphine with 1 mg butorphanol and 2 mL of normal saline (group 2), or 4 mg epidural morphine with 3 mg butorphanol (group 3). Patients were monitored for 24 h after administration of the study medications. There were no significant differences between the groups in visual analogue pain scores, time to first analgesic request, respiratory rate, or Trieger dot test performance in the 24 h immediately after these epidural injections. There were three patients in group 1 and one patient in group 2 who experienced oxygen saturations less than 90%. (No patients in group 3 developed an oxygen saturation less than 92%.) The patients in group 3 did not require treatment for pruritus or nausea, a response significantly different ($P < 0.001$ and $P < 0.05$, respectively) from group 1 or group 2. We conclude that 3 mg of butorphanol added to epidural morphine for postoperative analgesia after cesarean delivery decreases the occurrence of pruritus and nausea without significantly increasing respiratory depression or sedation, and without adversely affecting duration of analgesia.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—morphine, butorphanol. PAIN, POSTOPERATIVE—epidural morphine, butorphanol. ANALGESICS, MORPHINE, BUTORPHANOL.

Epidural narcotics are being used with increasing frequency for postoperative pain relief after cesarean delivery (1–7). Unfortunately, they may be associated with side effects including pruritus (20%–93% incidence) and nausea (8–11) (17%–60% incidence).

Stimulation of opioid receptors, specifically the μ-receptors, appears to cause pruritus and nausea (3,12–15). It is conceivable that a μ-receptor antagonist that also has analgesic receptor activation (κ-receptor), such as butorphanol, might reduce the occurrence of these side effects. In the absence of published studies testing the combination of morphine and butorphanol, we undertook a study to determine if the addition of butorphanol to morphine might decrease the incidence of side effects of epidural morphine without changing its analgesic efficacy in obstetrical patients.

Methods

This study was performed after approval by the Institutional Review Board and informed patient consent was obtained. All patients who required a cesarean delivery were considered for our study. We excluded patients receiving magnesium sulfate, patients who experienced a dural puncture, patients in whom epidural anesthesia for cesarean delivery was inadequate, and patients less than 18 yr of age. Thirty patients were randomized into three groups of 10 patients each, and the epidural solutions were given in a double-blinded fashion. All patients completed the study.

Lumbar epidural anesthesia was achieved using a

Received from the Department of Anesthesiology, Division of Experimental Medicine, St. Luke's Hospital, Kansas City, Missouri. Accepted for publication August 27, 1990.

Address correspondence to Dr. McNitt, Department of Anesthesiology, St. Luke's Hospital, Kansas City, MO 64111.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

standard technique. Lidocaine (2% with 1:400,000 epinephrine) was given incrementally to provide a sensory level of anesthesia to the fourth thoracic dermatome. After umbilical cord clamping, patients in group 1 received 4 mg preservative-free morphine and 3 mL preservative-free normal saline through the previously placed epidural catheter. In like manner, patients in group 2 were given 4 mg preservative-free morphine, 1 mg butorphanol, and 2 mL preservative-free normal saline. And, finally, patients in group 3 had 4 mg of preservative-free morphine and 3 mg epidural butorphanol injected. No patients received supplemental narcotics or sedatives intraoperatively. The epidural catheters were removed after the completion of surgery, and the patients were monitored for the next 24 h.

Patients were informed preoperatively that pruritus and nausea might occur and that treatment would be available at their request. Additional analgesics also were available upon request if the patient experienced pain during the 24-h observation period. This allowed the patient to control the administration of medication depending on the severity of side effects and adequacy of analgesia. The occurrence of pruritus or nausea and the treatment received were recorded. Patients requesting treatment for nausea and/or pruritus received 0.1 mg of naloxone and/or 25 mg of diphenhydramine intravenously, which was repeated if necessary. The presence of somnolence, defined as increased sleepiness or drowsiness, was recorded by nursing evaluation every hour. Psychomotor function was measured using the Trieger dot test (16,17) every 6 h. This test consists of asking patients to connect a series of dots on a previously constructed diagram using a pencil. The number of dots connected correctly by the patient is expressed as a percentage of the total number of dots in the diagram. The patients judged severity of pain using a 10-cm visual analogue pain scale, with 0 being "no pain" and 10 being "unbearable pain," every 6 h for 24 h. Duration of analgesia was measured as the time between epidural injection and the first request for pain medication. Respiratory status was evaluated by continuous pulse oximetry and by recording respiratory rate every 30 min for the first 4 h and hourly thereafter for 24 h. Oxygen saturation was continuously monitored for 24 h and recorded hourly or at any time it was less than 90%.

Analysis of variance for repeated measures and the Newman-Keuls test were used to evaluate visual analogue pain scale, respiratory rate, oxygen saturation, Trieger dot test, time to request for additional analgesia, pruritus, and nausea. Data are expressed as mean ± SEM unless otherwise noted. Statistical significance was defined as $P < 0.05$.

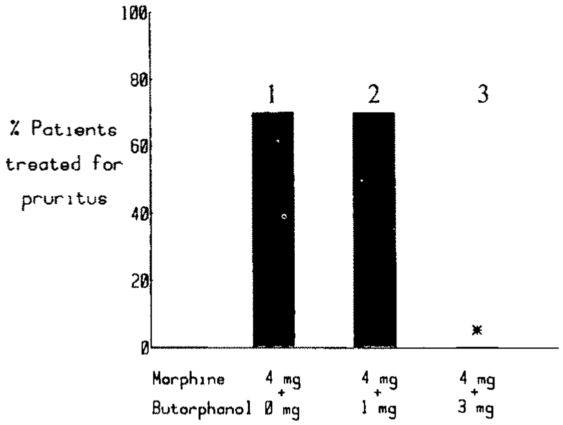


Figure 1. Incidence of pruritus. No patients in group 3 required treatment. *Significantly different as compared with group 1 or group 2, $P < 0.001$.

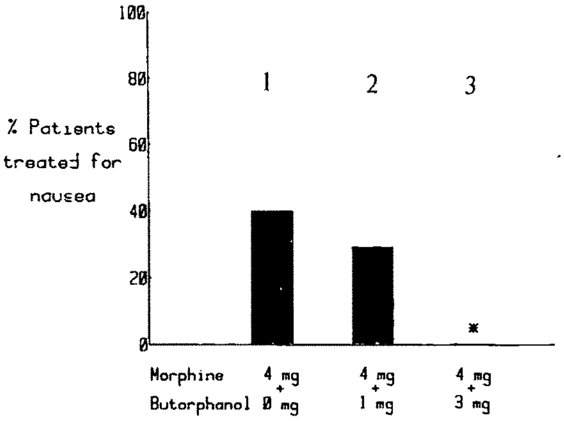


Figure 2. The incidence of nausea. No patients in group 3 required treatment. *Significantly different compared with group 1 or group 2, $P < 0.05$.

Results

All patients who agreed to participate completed the study. Operative anesthesia was adequate for the cesarean delivery in all patients.

The incidence of pruritus that required treatment was 70% in groups 1 and 2 (Figure 1). In contrast, none of the patients in group 3 required treatment for pruritus ($P < 0.001$ compared with groups 1 and 2). Nausea was absent in group 3 but occurred in 40% of the patients in group 1 and in 30% of the patients in group 2 ($P < 0.05$, Figure 2).

Visual analogue pain scores were not significantly different in the three groups at any time (Table 1), nor were the mean scores different (Table 2). In addition, there was no difference among the three groups in the time at which additional analgesic was first requested (Table 2). Somnolence occurred in none of the patients in any of the three groups during the 24-h observation period (Table 3). Psychomotor func-

Table 1. Visual Analogue Pain Scores

Group	Time (postoperative hour) 6	12	18	24
1	1.2	1.8	2.4	3.2
2	2.7	3.1	3.4	3.0
3	2.9	2.3	2.6	1.9

Values are expressed as mean scores.
There were no significant differences between groups at any time.

Table 2. Postoperative Analgesia

	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)
Visual analogue pain score	2.3 ± 0.22	3.0 ± 0.74	2.4 ± 0.66
Time to first narcotic	22.8 ± 0.89	23.0 ± 1.43	25.2 ± 1.36

Values are expressed as mean ± SEM.
There were no significant differences between groups at any time.

Table 3. Trieger Dot Test Scores and the Incidence of Somnolence

	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)
Trieger dot test (% correct)	79.0 ± 2.9	78.0 ± 3.47	80.7 ± 4.0
Incidence of drowsiness			
Objective	0	0	0
Subjective	0	0	0

Values are expressed as mean ± SEM.
There were no significant differences between groups at any time.

Table 4. Respiratory Indices

	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)
Spo_2 saturation (%)	94.6 ± 0.49	95.3 ± 0.46	95.8 ± 0.44
Respiratory rate	18.3 ± 0.76	17.2 ± 0.38	18.2 ± 0.63

Values are expressed as mean ± SEM.
There were no significant differences between groups at any time.
Spo_2 indicates oxygen saturation measured by pulse oximetry.

tion as measured by the Trieger dot test was not significantly different among the three groups (Table 3). Respiratory rate varied from 10 to 24 breaths/min during the study period; again, no differences were detected between the three groups (Table 4). The mean values for oxygen saturations were not statistically different (Table 4), but three patients in group 1 and one patient in group 2 required supplemental nasal oxygen to treat an oxygen saturation less than 90%. All patients in group 3 had oxygen saturations greater than 92% ($P < 0.05$ compared with groups 1 and 2).

Discussion

Epidural morphine administration has gained widespread use after cesarean delivery as a way to provide long-acting analgesia from a single injection (1–5). Despite this popularity, bothersome side effects have been observed. Bromage et al. (18) noted a 100% occurrence of pruritus with a 10-mg single bolus of morphine placed in the epidural space, compared with findings of Abboud et al. (19), Kotelko et al. (3), and Writer et al. (11), who showed an incidence of pruritus of 62%, 68%, and 93%, respectively, after 5 mg epidural morphine. Nausea occurs with varying frequency depending on the published reports—from 6.3% in Abboud et al. (19) to 53% in Writer et al. (11). Because pruritus and nausea are believed to be caused by μ-opioid receptor stimulation by morphine (10,11,13,14), we decided to test whether the addition of a weak μ-receptor antagonist (with κ-agonist activity) could reduce the incidence of pruritus and nausea after the administration of epidural morphine.

Our results suggest that the addition of 3 mg of butorphanol to 4 mg of morphine eliminates the need for treatment of pruritus and nausea after epidural administration.

The mechanism for the prevention of pruritus and nausea by butorphanol is probably μ-opioid receptor blockade. Our data suggest that analgesia is not decreased when butorphanol is added to morphine because butorphanol also stimulates the κ-receptor, which results in analgesia (12–15). This is probably a dose-dependent phenomenon, as the group that received 1 mg of epidural butorphanol did not differ from the control group with regard to side effects.

The duration of pain control as defined by the time to request for additional narcotics (Table 2) is similar to results reported by Bromage and coworkers for the duration of epidural morphine (20). The quality of pain control was not different between groups as shown by visual analogue pain scores (Table 2).

We were concerned that the addition of butorphanol could lead to more profound respiratory depression when compared with morphine used alone. Abboud et al. has demonstrated a decreased ventilatory response to carbon dioxide after both epidural butorphanol and epidural morphine (19), but they did not evaluate the combination of these two drugs. Gustafsson et al. (10) reported a retrospective study involving 6000 patients who underwent epidural or intrathecal opioid administration and showed a

0.33% incidence of respiratory depression as documented by the measurement of respiratory rates less than 10 breaths/min. These findings were later confirmed by Leicht et al. (21), who showed a 0.4% incidence of respiratory depression in 1000 patients, and Fuller et al. (22), who showed a 0.24% incidence in 4880 patients. Our study demonstrated that a number of patients who receive epidural morphine developed oxygen saturations less than 90%. Groups 1 and 2 included four patients with oxygen saturations less than 90% despite having respiratory rates considered to be adequate (respiratory rate greater than 10 breaths/min). These findings are consistent with the report of Brose and Cohen (23), who demonstrated a 71% incidence of oxygen saturation less than 85% after 5 mg of morphine administered epidurally. No patients in their study had a respiratory rate less than 10 breaths/min.

The addition of 3 mg butorphanol to epidural morphine appeared to prevent oxygen desaturation to less than 90% in group 3 ($P < 0.05$) compared with groups 1 and 2. This finding was both surprising and statistically significant. This again may be attributed to blockade of the μ-opioid receptors by butorphanol. Reduction in the incidence of desaturation after the addition of 3 mg butorphanol would appear to be consistent with the findings of Bowdle et al. (24), who showed increases in respiratory rate, tidal volume, minute ventilation, and ventilatory response to inspired carbon dioxide, and a decrease in arterial carbon dioxide, when butorphanol was given intravenously after fentanyl anesthesia. Although no significant differences were noted with regard to age, height, weight, or prior pulmonary and smoking history between groups, these factors cannot be excluded as a possible explanation. Perhaps pulse oximetry is a more sensitive clinical measure of epidural narcotic effect on respiration than is respiratory rate. A larger sample size would be required to reach a definite conclusion regarding the clinical utility of pulse oximetry as a method of monitoring the respiratory effect of epidurally placed opioids.

Previous studies have reported drowsiness, or "somnolence," after epidural butorphanol (19,25). Our patients did not complain of drowsiness nor did nursing personnel note a greater incidence of sedation in patients who received epidural butorphanol. This appears to diverge from the findings of Abboud et al. (19), who reported somnolence in 67% of patients receiving 4 mg of epidural butorphanol, in 72% of those receiving 2 mg butorphanol, in 48% receiving 1 mg butorphanol, and in 21% of patients receiving 5 mg epidural morphine. Evaluation of somnolence appears to differ in previous studies, probably due to variations in the measurement of somnolence.

In conclusion, we have shown that the addition of 3 mg of butorphanol to 4 mg of morphine placed in the epidural space appears to prevent pruritus and nausea after cesarean delivery without affecting the quality or duration of analgesia and without increasing the incidence of respiratory depression. We were not able to document additive respiratory depressant effects, however; a larger study should be done to confirm this finding.

In addition, the use of continuous pulse oximetry as a method of monitoring patients after epidurally placed opioids may have clinical efficacy.

The authors thank Gigi Perry of Ohmeda Corp., who donated use of the pulse oximeters, Tim Cussen, CRNA, Mary Isbell, Crystal Ewing, Mary Brinkman, and Evelyn Bulan, pain consultant nurses, and the postpartum nursing staff of St. Luke's Hospital. The authors also thank St. Luke's Hospital Medical Education Research Fund for providing funds for this investigation, and Lisa Young for her patience and help in the preparation of this manuscript.

References

1. Coombs DW, Danielson DR, Pageau MC, Rippe E. Epidurally administered morphine for post-cesarean analgesia. Surg Gynecol Obstet 1982;154:385–8.
2. Chadwick HS, Ready LB. Intrathecal and epidural morphine sulphate for post cesarean section analgesia. Anesthesiology 1988;68:925–9.
3. Kotelko DM, Dailey PA, Shnider SM, Rosen MA, Hughes SC, Brizgys RV. Epidural morphine analgesia after cesarean delivery. Obstet Gynecol 1984;63:409–13.
4. Ross BK, Hughes SC. Epidural spinal narcotic analgesia. Clin Obstet Gynecol 1987;30:552–65.
5. Rosen MA, Hughes SC, Shnider SM, et al. Epidural morphine for the relief of postoperative pain after cesarean section. Anesth Analg 1983;62:666–72.
6. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.
7. Behar M, Oeshwang D, Mayora F, Davidson JT. Epidural morphine in treatment of pain. Lancet 1979;ii:527–9.
8. Torda TA, Pybus DA. Comparison of four narcotic analgesics for extradural analgesia. Br J Anaesth 1982;54:291–5.
9. Carmichael FJ, Rolbin SH, Hew EM. Epidural morphine for analgesia after caesarean section. Can Anaesth Soc J 1982;29: 359–63.
10. Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. Br J Anaesth 1982;54:479–86.
11. Writer WDR, Hurtig JB, Edelist G, et al. Epidural morphine prophylaxis of postoperative pain: report of a double-blind multi-center study. Can Anaesth Soc J 1985;32:330–8.
12. Way EL. Sites and mechanisms of basic narcotic receptor function based on current research. Ann Emerg Med 1986;15: 1021–5.

13. Martin WR. Clinical evidence for different narcotic receptors and relevance for the clinician. Ann Emerg Med 1986;15: 1026–9.
14. Yaksh TL. Opioid receptor systems and the endorphins: a review of their spinal organization. J Neurosurg 1987;67:157–76.
15. Justins DM, Knott C, Luthman J, Reynolds F. Epidural versus intramuscular fentanyl. Analgesia and pharmacokinetics in labor. Anaesthesia 1983;38:937–42.
16. Trieger N, Newman MG, Miller JC. An objective measure of recovery. Anesth Prog 1969;16:4–7.
17. Newman MG, Trieger N, Miller JC. Measuring recovery from anesthesia—a simple test. Anesth Analg 1969;48:136–40.
18. Bromage PR, Camporesi EM, Durant PAC, Nielsen CH. Nonrespiratory side effects of epidural morphine. Anesth Analg 1982;61:490–5.
19. Abboud TK, Moore M, Zhu J, et al. Epidural butorphanol or morphine for the relief of post-cesarean section pain: ventilatory responses to carbon dioxide. Anesth Analg 1987;66:887–93.
20. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1980;50:473–80.
21. Leicht CH, Hughes SC, Dailey PA, Shnider SM, Rosen MA. Epidural morphine sulfate for analgesia after cesarean section: a prospective report of 1000 patients (abstract). Anesthesiology 1986;65:A366.
22. Fuller JG, McMorland GH, Couglas J, Palmer L, Constantine LV. Epidural morphine for postoperative pain after caesarean section: a review (abstract). Proc Soc Obstet Analg Perinatol 1988;20:94.
23. Brose WG, Cohen SE. Oxyhemoglobin saturation following cesarean section in patients receiving epidural morphine, PCA, or IM meperidine analgesia. Anesthesiology 1989;70: 948–53.
24. Bowdle TA, Greichen SL, Bjurstrom RL, Schoene RB. Butorphanol improves CO_2 response and ventilation after fentanyl anesthesia. Anesth Analg 1987;66:517–22.
25. Hunt CO, Naulty JS, Malinow AM, Datta S, Ostheimer GW. Epidural butorphanol-bupivacaine for analgesia during labor and delivery. Anesth Analg 1989;68:323–7.

Efficacy of Ephedrine in the Prevention of Postoperative Nausea and Vomiting

David M. Rothenberg, MD, Samuel M. Parnass, MD, Kim Litwack, PhD, RN,
Robert J. McCarthy, PharmD, and L. Michael Newman, MD, PhD

ROTHENBERG DM, PARNASS SM, LITWACK K, McCARTHY RJ, NEWMAN LM. Efficacy of ephedrine in the prevention of postoperative nausea and vomiting. Anesth Analg 1991;72:58–61.

Although reported in the aerospace literature and anecdotally by anesthesiologists, the putative antiemetic effect of ephedrine remains unquantitated. We therefore prospectively studied ephedrine as an antiemetic agent in the perioperative setting in 97 patients undergoing general anesthesia for outpatient gynecologic laparoscopy. Patients were assigned in a double-blind randomized fashion to receive a standardized general anesthetic followed by an intramuscular dose of either ephedrine (0.5 mg/kg), droperidol (0.04 mg/kg), or saline before the conclusion of surgery. Nausea, retching, or vomiting, as well as the degree of sedation and discharge times, were assessed in the recovery room and for 24 h postoperatively. Ephedrine was found to have a significantly antiemetic effect ($P < 0.05$) when compared with placebo and an antiemetic effect similar to that of droperidol. Sedation scores were also significantly less in the ephedrine group than in both placebo and droperidol groups. Finally, variations in mean arterial blood pressure among the three groups were not statistically significant. We conclude that ephedrine is an effective antiemetic agent with minimal sedative side effects in patients undergoing outpatient laparoscopy.

Key Words: VOMITING, POSTOPERATIVE—ephedrine. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—ephedrine, antiemetic effects.

The incidence of postoperative nausea and vomiting in ambulatory surgery has been reported to be as high as 50% (1,2). Surgical procedures such as laparoscopy, therapeutic abortions, orchiopexy, varicocelectomy, or strabismus surgery are associated with an especially high incidence of nausea and vomiting (1,3–6). In an ambulatory surgery population this may prove to be an especially difficult problem, with early discharge from the ambulatory unit often being precluded by postoperative nausea and vomiting, or by the sedative side effects of currently used antiemetic agents. The prophylactic use of ephedrine as an antiemetic agent has been described for the prevention of motion sickness (7,8). Although ephedrine has been utilized in treating nausea and vomiting in the postanesthesia recovery rooms, especially in patients whose symptoms are related to their assuming an upright position (B. V. Wetchler, personal communication), there are at present no controlled studies assessing the effect of ephedrine in preventing nausea and vomiting after general anesthesia. This study was therefore designed to determine the antiemetic effect of ephedrine in a prospective, randomized, and double-blinded fashion in patients undergoing outpatient gynecologic laparoscopy.

Methods

After approval of our institution's Human Investigation Committee, informed consent was obtained from 100 ASA physical status I or II patients undergoing outpatient gynecologic laparoscopy. Exclusion criteria included patients with a history of hypertension or organic heart disease, and patients being treated preoperatively with medications with potential antiemetic effects (e.g., benzodiazepines, steroids, droperidol, scopolamine, antihistamines, or metoclopramide).

After preoxygenation and defasciculation with 3 mg intravenous (IV) *d*-tubocurare, induction of anesthesia was achieved with 5 mg/kg IV thiopental

---

Received from the Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois. Accepted for publication August 24, 1990.

Address correspondence to Dr. Rothenberg, Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, 739 Jelke, 1750 West Congress Parkway, Chicago, IL 60612.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

followed by endotracheal intubation facilitated with 1.5 mg/kg IV succinylcholine. Positive pressure ventilation by mask was avoided before intubation so as to minimize gastric distention. All patients received 2 μg/kg IV fentanyl as part of a balanced anesthetic technique and to provide postoperative analgesia. Anesthesia was maintained with hemodynamically adjusted levels of isoflurane in nitrous oxide (70%) and oxygen (30%). Muscle relaxation in accordance with surgical needs was achieved with intermittent doses of vecuronium. No other anesthetic agents or intraoperative medications were used. All patients received IV infusions of lactated Ringer's solution in quantities determined to be appropriate by the anesthesiologist.

Before reversal of neuromuscular blockade with 0.07 mg/kg IV neostigmine and 0.01–0.02 mg/kg IV glycopyrolate, a blinded dose of either placebo (0.9% saline intramuscular [IM]), 0.04 mg/kg IM droperidol, or 0.5 mg/kg IM ephedrine was administered. All doses were prepared in equal volumes, and all IM injections were made into the deltoid muscle using a 22-gauge needle.

In the recovery room the patients were evaluated every 5–10 min for nausea, retching, or vomiting by a nurse not directly involved in the study. If a patient experienced some or all of these signs or symptoms, she was categorized by the most severe sign or symptom (i.e., if the patient had nausea and vomiting, she was classified as vomiting). Nausea was assessed by the recovery room nurse asking "Do you have any complaints?" Sedation was assessed using a three-point scale: 0, unarousable; 1, lethargic; 2, alert. Nausea, retching, vomiting, or pain were treated at the discretion of the patient's anesthesiologist. The type and dosage of antiemetic or analgesic administered were documented. Time between arrival in the recovery room and the ability to ambulate without symptoms, as well as the time to discharge, were recorded, as were total IV fluids. Mean arterial pressure and heart rate were recorded every 5–10 min.

Within 24 h a telephone call was made to each patient to inquire about the above or additional postoperative symptoms.

Ordinal data were analyzed by χ^2 and interval data by analysis of variance. Significance was accepted at $P < 0.05$.

Results

Of the 100 patients studied, three patients required laparotomy and were therefore excluded from the study. Of the remaining 97 patients, 33 were assigned to the placebo group, 32 to the droperidol group, and 32 to the ephedrine group. There were no differences in regard to age, weight, amount of IV fluids administered, or duration of anesthesia between the three groups (Table 1).

Table 1. Group Demographics

Group	Saline	Droperidol	Ephedrine	*P*
n	33	32	32	
Age (yr)	32 ± 6	31 ± 6	30 ± 6	0.32
Weight (kg)	68 ± 15	62 ± 13	66 ± 9	0.30
Length of anesthesia (min)	64 ± 34	59 ± 23	68 ± 23	0.41
Fluids in operating room (mL)	1059 ± 476	960 ± 262	1132 ± 446	0.31

Table 2. PACU and Follow-up Results

Group	Saline	Droperidol	Ephedrine	*P*
PACU				
Total nausea/retch/vomit	66.7	37.5[a]	34.4[b]	0.01
Antiemetic treatment (%)	51.5	18.8[a]	21.9[b]	0.01
Sedation (%)	36.4[c]	65.6	6.3[b,d]	<0.01
Discharge time (min)	91 ± 39	97 ± 51	76 ± 39	0.08
Mean arterial pressure (mm Hg)				0.17
Time 0	102 ± 13	94 ± 19	99 ± 10	
30 min	99 ± 10	92 ± 12	92 ± 9	
Discharge	92 ± 11	88 ± 14	86 ± 11	
Follow-up				
Vomit at home (%)	9.1	6.3	6.3	0.88

[a] $P < 0.05$ compared with saline data.
[b] $P < 0.05$ compared with saline data.
[c] $P < 0.05$ compared with droperidol data.
[d] $P < 0.05$ compared with droperidol data.

The incidence of nausea, retching, and vomiting in both the recovery room and at home appears in Table 2. Ephedrine was as effective as droperidol, and both were significantly more effective than placebo in minimizing nausea and vomiting. Patients in both the droperidol and ephedrine groups required significantly less antiemetic therapy in the immediate postoperative period. Also, patients who received ephedrine had significantly lower sedation scores than patients given either droperidol or saline ($P < 0.01$) (Table 2). A trend toward shorter discharge time was noted in the ephedrine group ($P = 0.08$); however, statistical significance was not achieved. Finally, there were no significant differences among the three groups with regard to mean arterial pressure. Follow-up evaluation of the patients at home showed no significant differences in the incidence of vomiting, nor were any other untoward events noted (e.g., severe nausea, prolonged sedation, dystonic reactions, or palpitations).

Discussion

The prevention and treatment of nausea and vomiting after general anesthesia for outpatient surgery continues to pose significant problems for both patients and ambulatory surgery units. Nausea and vomiting are among the most common complications of outpatient surgery and the number one nonsurgical reason for unexpected admission to the hospital (9). Previous studies have reported varying success rates with different antiemetic therapies (10–12). Sedation due to large dosages of antiemetics may delay discharge from a recovery room, and late side effects with droperidol, such as anxiety and restlessness, have been reported in ambulatory surgery patients (13). In our study we attempted to evaluate the efficacy of ephedrine as a nonsedating antiemetic agent for preventing nausea and vomiting after outpatient gynecologic laparoscopy.

Ephedrine, a sympathomimetic drug, was found by Wood and Graybiel as early as 1968 to be effective in preventing motion sickness (7). Studying the effects of scopolamine on motion sickness in healthy naval volunteers, they gave ephedrine with scopolamine in an attempt to counteract the sedative side effects of scopolamine. They found that not only was the combination effective in minimizing motion sickness, but that ephedrine alone (administered in a control group) also had a significant antiemetic effect. Other sympathomimetic drugs have been reported in the early literature to be effective in treating motion sickness (7). The beneficial effects of these agents is bolstered by the fact that phenoxybenzamine, a sympatholytic drug, causes symptoms that mimic true motion sickness. Motion sickness is believed to be caused by a disequilibrium in the vestibular apparatus that, in turn, sends afferent impulses to the chemoreceptor trigger zone via cholinergic and histaminic fibers and thence to the vomiting center (8). Whether this pathway is ultimately responsible for the nausea and vomiting seen after surgery and anesthesia is only speculative. A high degree of vagal tone in the perioperative period may also add to the incidence of postoperative nausea and vomiting, and ephedrine may minimize these symptoms by increasing sympathetic tone. This is presumed to be the mechanism by which the parasympatholytic agent scopolamine acts to prevent nausea and vomiting (14).

Finally, hypotension during spinal or epidural anesthesia, is often heralded by nausea and vomiting. This has been ascribed in part to a reduction in medullary blood flow to the chemoreceptor trigger zone (15), and therefore ephedrine is commonly employed to increase mean arterial pressure and presumably improve medullary blood flow, thus minimizing these symptoms. An increase in gastric peristalsis due to preganglionic sympathetic denervation of the stomach may also provoke nausea and vomiting during spinal anesthesia (16), but whether ephedrine could mitigate this mechanism remains unknown. Ephedrine may also have beneficial effects in minimizing the nausea and vomiting associated with postural hypotension after outpatient surgery. These signs and symptoms may occur after general anesthesia, especially with ambulation, due either to intravascular volume depletion or to residual vasodilation from potent inhalation anesthetics, or both.

Concerns about the prophylactic use of ephedrine in patients with hypertension or organic heart disease are valid; therefore, we avoided its use in such patients so as to minimize the risk of potential myocardial or cerebrovascular damage. In otherwise healthy patients the risks of prophylactic ephedrine appear to be minimal. Phenylpropanolamine, a racemic form of norephedrine, has been anecdotally reported to cause transient elevations in blood pressure (17) and cerebrovascular complications after higher doses in susceptible patients (18,19). Most of these studies, however, were done with small numbers of patients, without controls, and with large doses of phenylpropanolamine. A more recent multicenter, double-blind study failed to show any significant hemodynamic response with a 75-mg dose of phenylpropanolamine when administered on a short-term basis (20).

This study demonstrates that ephedrine is an effective prophylactic antiemetic agent in patients having general anesthesia for outpatient laparoscopy. It may be particularly indicated as prophylaxis in patients prone to motion sickness or for those in whom dizziness, nausea, and/or vomiting occur upon ambulation postoperatively. Its mechanism of action as an antiemetic is uncertain, but when compared with a relatively high dose of droperidol it is equally effective and minimizes sedation.

References

1. Wetchler BV. Problem solving in the PACU. In: Wetchler BV, ed. Anesthesia for ambulatory surgery. Philadelphia: Lippincott, 1985:275–316.
2. Rising S, Dodgson MS, Steen PA. Isoflurane v. fentanyl for

outpatient laparoscopy. Acta Anaesthesiol Scand 1985;29: 251–5.

3. Pataky AO, Kitz DS, Andrews RW, Lecky JH. Nausea and vomiting following ambulatory surgery: are all procedures created equal? Anesth Analg 1988;67:S163.
4. Smessaert A, Schehr C, Artusio J. Nausea and vomiting in the immediate post anesthetic period. JAMA 1959;170:2072–6.
5. Caldamone AA, Rabinowitz R. Outpatient orchiopexy. J Urol 1982;127:286.
6. Bonica JJ, Crepps W, Mark B, et al. Postoperative nausea, retching and vomiting. Anesthesiology 1958;19:532–40.
7. Wood CD, Graybiel A. Evaluation of sixteen anti-motion sickness drugs under controlled laboratory conditions. Aerospace Med 1968;39:1341–4.
8. Wood CD. Antimotion sickness and antiemetic drugs. Drugs 1979;17:471–9.
9. Gold BS, Kitz DS, Lecky JH, Neuhaus JM. Unanticipated admission to the hospital following ambulatory surgery. JAMA 1989;262:3008–10.
10. Madaj TH, Simpson KH. Comparison of the use of domperidone, droperidol and metoclopramide in prevention of nausea and vomiting following gynaecological surgery in day cases. Br J Anaesth 1986;58:879–83.
11. Kortilla K, Kauste A, Auvinen J. Comparison of domperidome, droperidol and metoclopramide in prevention and treatment of nausea and vomiting after balanced general anesthesia. Anesth Analg 1979;58:396–400.
12. Cohen SE, Woods WA, Wyne J. Antiemetic efficacy of droperidol and metoclopramide. Anesthesiology 1984;60:67–9.
13. Melnick B, Sawyer R, Karambelkar D, Phitayakorn P, Lim Uy NT, Patel R. Delayed side effects of droperidol after ambulatory general anesthesia. Anesth Analg 1989;69:748–51.
14. Bailey PL, Bubbers SJM, East KA, Posthuma WFM, Stanley TH. Transdermal scopolamine reduces postoperative nausea and vomiting. Anesthesiology 1988;69:A641.
15. Covino BG, Lambert DH. Epidural and spinal anesthesia. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical anesthesia. Philadelphia: Lippincott, 1989;755–86.
16. Greene NM. Physiology of spinal anesthesia. 3rd ed. Baltimore: Williams & Wilkins, 1981:258–60.
17. Lake CR, Zaloga G, Clymer F, Quirk FM, Chernow B. A double dose of phenylpropanolamine causes hypertension. Am J Med 1988;85:339–43.
18. Kase CS, Foster TE, Reed JE, Spatz EL, Girgis GN. Intracerebral hemorrhage and phenylpropanolamine use. Neurology 1987;37:399–404.
19. McDowell JR, LeBlanc HJ. Phenylpropanolamine and cerebral hemorrhage. West J Med 1985;142:688–91.
20. Blackburn GL, Morgan JP, Lavin PT, Noble R, Funderburk FR, Istfan N. Determinants of the pressor effect of phenylpropanolamine in healthy subjects. JAMA 1989;261:3267–72.

Electrophysiologic Effects of Bupivacaine in the Isolated Rabbit Heart

Pierre Lacombe, MD, Gilbert Blaise, MD, Didier Loulmet, MD, and Charleen Hollmann, RN

LACOMBE P, BLAISE G, LOULMET D, HOLLMANN C. Electrophysiologic effects of bupivacaine in the isolated rabbit heart. Anesth Analg 1991;72:62–9.

To assess the direct electrophysiologic effects of bupivacaine, we examined the spontaneous sinus rhythm and induced rapid and premature atrial and ventricular pacing in 11 isolated rabbit hearts perfused in the Langendorff apparatus with varying concentrations (designated by [ ]) of bupivacaine (control, n = 2; 0.3 μg/mL, n = 3; 1.5 μg/mL, n = 3; 3.0 μg/mL, n = 3). There was no change in sinus node automaticity or sinus node recovery time at any concentration and no evidence of abnormal automaticity. Depression of conduction was reflected by prolongation of the PR interval at the following concentrations: 1.5 μg/mL (65.0 ms before, 96.6 ms after) and 3.0 μg/mL (61.6 ms before, 103.3 ms after) and increase in atrial and ventricular pacing thresholds at 3.0 μg/mL (atrial: 0.86–8.6 mA, ventricular: 2.0–10.0 mA). No spontaneous tachyarrhythmias occurred; 2:1 spontaneous atrioventricular block (n = 1) and a decrease in maximal paced rate with 1:1 anterograde or retrograde atrioventricular conduction were noted at all concentrations of bupivacaine. Thus bupivacaine did not change automaticity but had a depressant effect on conduction at the atrial, ventricular, and atrioventricular levels, providing a basis for clinically occurring atrioventricular block and reentrant arrhythmias.

Key Words: ANESTHETICS, LOCAL—bupivacaine, cardiac toxicity. HEART, ELECTROPHYSIOLOGY—bupivacaine effects.

Bupivacaine is a commonly used potent amide-type local anesthetic. At high plasma levels of bupivacaine, cardiac toxicity occurs, manifested by abnormalities of contractile function as well as rhythm disturbances (1–14). These adverse effects can be severe, sometimes lethal (15,16); however, the nature and mechanisms of the arrhythmias occurring in such a setting are not completely defined.

Bupivacaine-induced abnormalities of contractility and metabolism have been studied in the isolated heart (17); we used the same experimental method to determine whether arrhythmias are directly caused by the drug, to define the nature of these arrhythmias, and to identify their underlying mechanisms.

Methods

These experimental data were collected from 11 isolated rabbit heart preparations collected from animals in which anesthesia was induced with a short-acting barbiturate and a thoracotamy performed to expose the heart and cannulate the ascending aorta with a centrally directed perfusion catheter placed with its end just above the aortic valve. The venae cavae, pulmonary artery, pulmonary veins, and ascending aorta were cut, and the heart was removed and suspended in a Langendorff apparatus by the perfusion cannula. The oxygenated (95% O_2, 5% CO_2) perfusion solution (119 mM NaCl, 4.2 mM KCl, 1.3 mM $CaCl_2 \cdot 2H_2O$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4 \cdot 7H_2O$, 25 mM $NaHCO_3$, 15 mM glucose) was administered at constant pressure (85 cm H_2O) and temperature (37°C). The solution entered the heart through the coronary arteries only. The perfusion rate was measured by collecting the solution dripping from the heart. This flow rate was used to adjust the perfusion rate of the drug, which was pumped via a 25-gauge needle directly into the perfusion cannula, a few centimeters above the heart.

Using a multichannel oscilloscope (E for M, VR-6, Honeywell) attached to an ink-jet printer with adjustable recording speed (Siemens-Elema, Mingograf), the following electrical signals were continuously recorded.

Received from the Departments of Cardiology, Anesthesiology, and Cardiovascular Surgery, Notre-Dame Hospital, University of Montreal, Montreal, Quebec, Canada. Accepted for publication August 24, 1990.

Address correspondence to Dr. Blaise, Department of Anesthesiology, Notre Dame Hospital, 1560 Sherbrooke East, Montreal, Quebec, Canada, H2L 4M1.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

1. Local epicardial electrograms of each of the four cardiac chambers obtained through four pairs of implanted needle electrodes (Grass electrodes) placed on the lateral free wall of the ventricles and the anterior aspect of the atria.
2. Local endocardial electrograms in the vicinity of the atrioventricular (AV) junction: a 7F quadripolar catheter with 5-mm interelectrode spacing (Josephson type) was advanced via the superior vena cava to the right ventricle. When a stable position was obtained, recordings were made from each pair of adjacent electrodes (1–2, 2–3, 3–4); the signal showing the shortest time interval between atrial and ventricular activation, and considered closest to the AV junction, was selected. This "junctional" electrogram was further validated by observing the sequence of atrial activity in sinus rhythm.
3. A "surface" electrocardiogram (ECG) was obtained by connecting the arm electrodes of an ECG-recording system to a wet gauze sponge wrapped around the whole preparation (the leg electrodes were grounded).

Standard ECG filters were used for the "surface" tracing; epicardial and endocardial signals were filtered between 30 and 500 Hz.

Bipolar pacing was performed via the epicardial electrodes with a programmable stimulator (Bloom and associates), using rectangular impulses of 1-ms duration at an amplitude equal to twice the pacing threshold of the right atrium or left ventricle. The protocol consisted of rapid atrial or ventricular stimulation using impulse trains of 15–30-s duration at an initial cycle length of 300 ms, which was progressively decreased by 10–20 ms from sequence to sequence until 1:1 capture of the paced chamber was no longer possible. This allowed assessment of sinus node recovery time and maximal paced cycle length at which 1:1 conduction from the paced to the nonpaced chambers ceased to occur (the anterograde and retrograde Wenckebach points); in addition, a train of eight impulses was delivered to the right atrium at a cycle length less than 10% below the spontaneous sinus cycle length to allow determination of the sinoatrial conduction time.

The protocol also consisted of premature atrial and ventricular stimulation. A train of eight impulses at a cycle length of 250 ms was followed by a premature impulse, initially set at 240 ms from the last impulse; this prematurity interval was decreased in the following sequences by 10 ms until the premature impulse failed to capture the paced chamber. This allowed the determination of the functional and effective refractory periods of the atrium, the ventricle, and the AV junction. In addition, premature ventricular stimulation introduced a second premature impulse, also progressively more premature until it no longer captured the ventricle (the first premature impulse in the sequence was set 20 ms above the ventricular refractory period) in an attempt to induce ventricular tachyarrhythmias.

The whole protocol was completed and then repeated in its entirety during infusion of various concentrations: bupivacaine 0.3 μg/mL (n = 3), 1.5 μg/mL (n = 3), 3.0 μg/mL (n = 3), or 0 = normal saline used as a placebo (n = 2). After completing the second phase, an attempt was made to induce ventricular fibrillation using very rapid trains of rapid ventricular stimulation at cycle lengths of 10–250 ms using 10-mA impulses of 5-ms duration; however, this was unsuccessful.

Definitions

Results are expressed using the standard definitions used in clinical electrophysiology (18) with the exception of "AV junction" refractory periods (functional and effective), a term we used in place of "AV nodal" because the absence of a His bundle recording (sometimes thought to be present, but inconstant and not validated by previous literature) localization to the AV node is uncertain. Thus, AV junction effective refractory period is the maximum interval of prematurity of a paced chamber impulse failing to conduct to the nonpaced chamber through the AV junction. Atrioventricular junction functional refractory period is the minimum degree of prematurity achieved in the nonpaced chamber by sending premature impulses to the paced chamber.

In addition to usual ECG intervals, we also measured (Figure 1) AV interval (from the onset of atrial to the onset of ventricular activity in the intracardiac lead) and the AA interval (from the onset of right atrial activity to the onset of left atrial activity during sinus rhythm).

Statistical analysis was done using one-way analysis of variance with Tukey's multiple comparison test.

Results

Measurements in Sinus Rhythm

No significant change was seen for any parameters at 0 and 0.3 μg/mL (Table 1, Figure 2). Sinus cycle

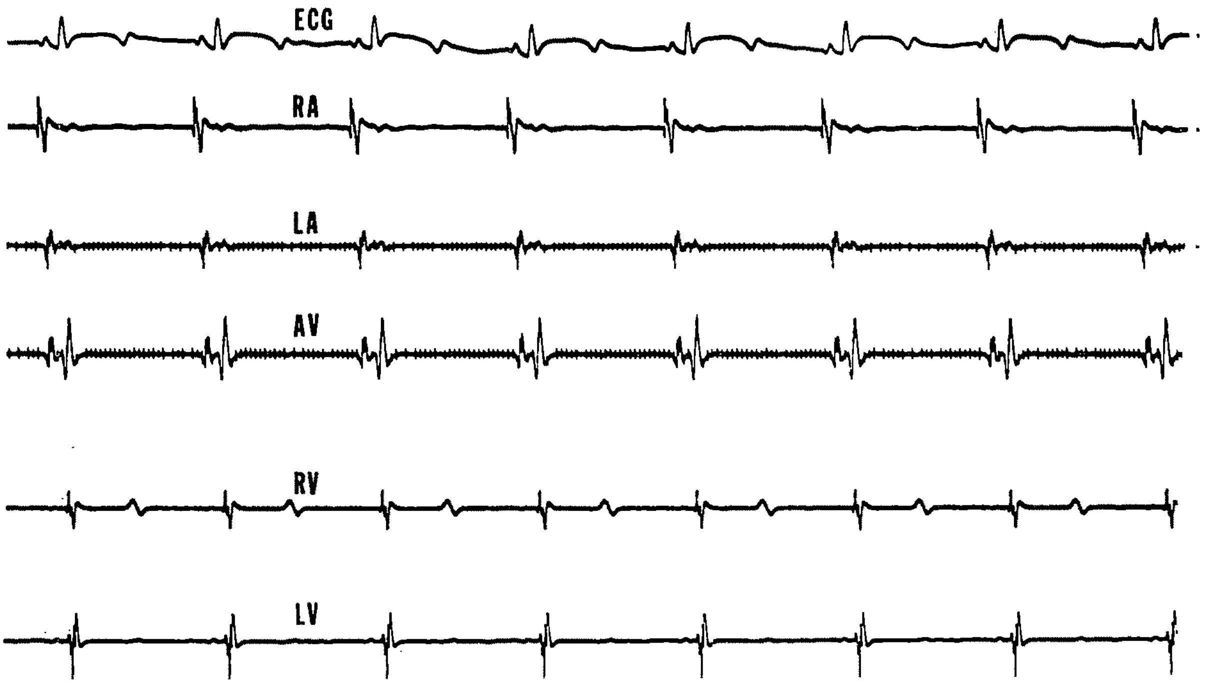


Figure 1. Recordings in sinus rhythm. ECG, electrocardiogram; RA, right atrium; LA, left atrium; AV, atrioventricular junction; RV, right ventricle; LV, left ventricle.

length was unaffected at all concentrations. Duration of the P wave and AA interval increased at 3.0 μg/mL. Compared with baseline, this increment was 24% for P wave and 22% for AA interval. The QRS complex showed a similar trend, with an increase of 48% at 1.5 μg/mL and 56% at 3.0 μg/mL, whereas the QT interval was significantly increased by 28% at 3.0 μg/mL. After calculating QTc using the formula $QTc = QT/\sqrt{RR}$, the increment (25%) was also significant only at 3.0 μg/mL. The statistically significant increase in PR and AV interval duration was of greater magnitude and occurred at both 1.5 μg/mL (PR increases 49%, AV increases 41%) and 3.0 μg/mL (PR increases 127%, AV increases 118%).

Response to Rapid Pacing

No change occurred for any parameter at 0 μg/mL (Table 2). Corrected sinus node recovery time and sinoatrial conduction time were unchanged at all concentrations. Pacing thresholds were increased at 1.5 and 3.0 μg/mL for both atrium and ventricle (Figure 3), frequently exceeding the maximal output

Table 1. Measurements in Sinus Rhythm[a]

	[0]				[0.3]						[1.5]						[3.0]					
	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B
SCL	340	330	350	310	350	360	400	380	370	380	310	330	360	370	320	320	350	410	390	385	370	385
P	35	35	30	30	40	45	45	55	50	55	60	70	45	90	34	45	45	75	40	45	40	45
QRS	50	55	45	50	50	60	60	55	50	50	60	90	45	80	50	60	50	90	55	75	45	70
PR	45	45	50	55	60	60	80	80	55	60	80	110	45	100	70	80	60	220	70	120	55	80
QT	220	220	210	220	210	230	300	275	220	210	220	250	220	250	215	210	250	430	330	350	240	275
QTc	377	383	355	395	355	383	474	446	362	341	395	435	366	411	380	371	423	672	528	564	390	443
AA	55	55	55	55	55	50	40	40	45	45	50	65	40	70	50	45	50	75	45	65	60	65
AV	60	60	70	70	70	70	85	80	70	70	80	100	70	130	70	80	65	220	70	115	60	90

Square brackets, [ ], denote bupivacaine concentration in micrograms per milliliter; C, control measurements; B, measurements after bupivacaine administration.

Intervals (SCL, P, QRS, PR, QT, QTc, AA, AV) are defined in the text.

[a] Data are from each individual heart before and after bupivacaine. All values are expressed in milliseconds.

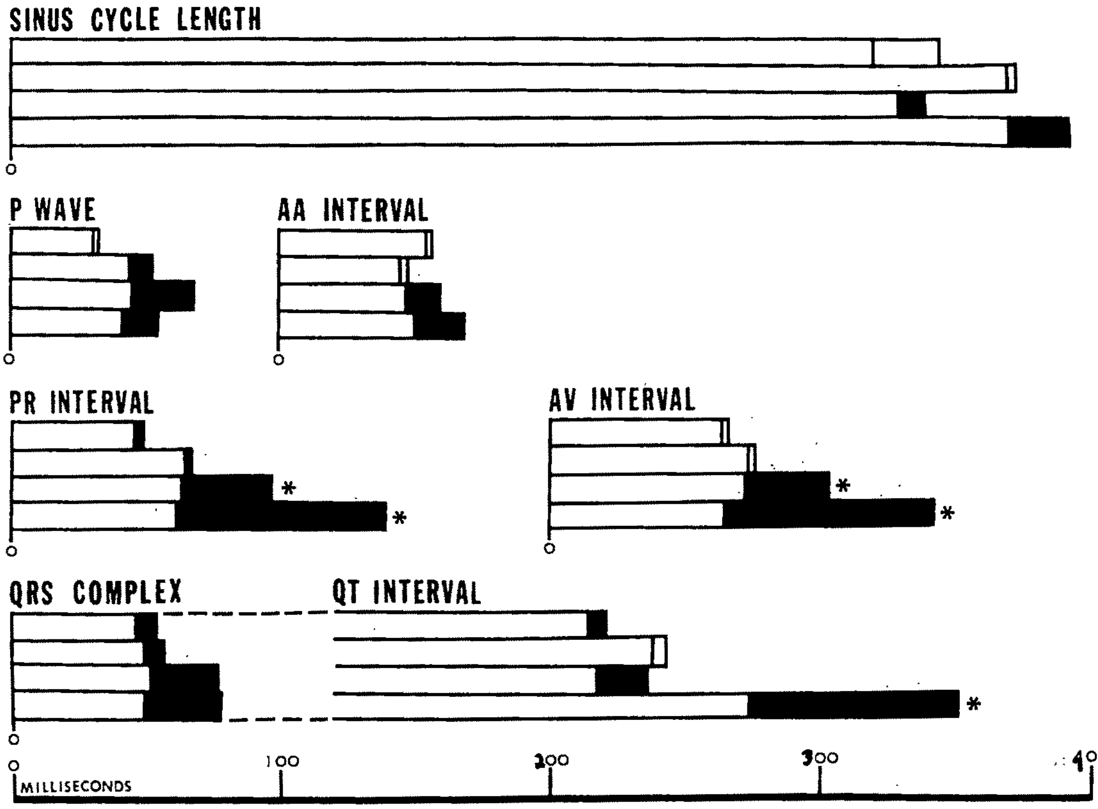


Figure 2. Effects of bupivacaine on electrographic intervals during sinus rhythm. For each value the four bars represent from top to bottom the effects of 0, 0.3, 1.5, and 3.0 μg/mL. *Significant at the 0.05 level.

of the stimulator (10 mA × 5 ms). This precluded further stimulation studies. The minimal cycle at which 1:1 capture could be maintained (Figure 4) was significantly increased in the ventricle at 0.3 μg/mL (no change was seen in the atrium) but could not be determined at 1.5 and 3.0 μg/mL. The point of Wenckebach (longest paced atrial cycle length inducing physiologic AV block) (Figure 5) was significantly increased in the anterograde direction at 1.5 μg/mL; at 3.0 μg/mL, a spontaneous Wenckebach phenomenon occurred in sinus rhythm in one experiment. In

Table 2. Electrophysiologic Data[a]

	[0]				[0.3]						[1.5]						[3.0]					
	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B
A Threshold	1.1	0.6	0.2	0.2	0.3	0.3	2.0	5.0	1.6	1.3	0.5	0.6	0.5	1.5	0.8	10+	0.3	5.8	0.3	10+	20	10+
V Threshold	2.2	2.3	2.5	3.0	0.5	0.5	2.0	5.0	3.2	0.5	0.6	7.9	2.3	10+	0.4	10+	2.1	10+	2.0	10+	20	10+
A 1:1 min	170	160	160	150	130	140	140	150	100	110	140	220	140	290	160	—	150	—	—	—	180	—
V 1:1 min	180	190	140	160	160	210	160	250	170	190	210	260	220	—	220	—	170	—	250	—	150	—
Ant W	170	170	160[b]	150	150	150	170	170	130	170	150	300	150	310	160[b]	—	190	410	220	—	180[b]	—
Ret W	190	190[b]	150	160	170	210	200	260	170[b]	190[b]	210[b]	300	220[b]	—	220[b]	—	170[b]	—	250[b]	—	180[b]	—
CSNRT	40	30	40	35	40	40	70	80	70	70	30	40	40	60	30	—	30	70	50	—	60	—
SACT	30	30	20	30	30	35	40	70	0	40	25	20	70	50	20	—	40	—	30	—	50	—

Square brackets, [ ], denote bupivacaine concentration in micrograms per milliliter; C, control measurements; B, measurements after bupivacaine administration; A, atrial; V, ventricular; 1:1 min, minimum cycle length with 1:1 capture; Ant W, Ret W, anterograde and retrograde Wenckebach cycles, respectively; CSNRT, corrected sinus node recovery time; SACT, sinoatrial conduction time; 10+, threshold superior to 10 mA.

[a] Data are from each individual heart before and after bupivacaine. Thresholds are expressed in milliamperes. All other values are expressed in milliseconds.

[b] Wenckebach cycle inferior or equal to given value.

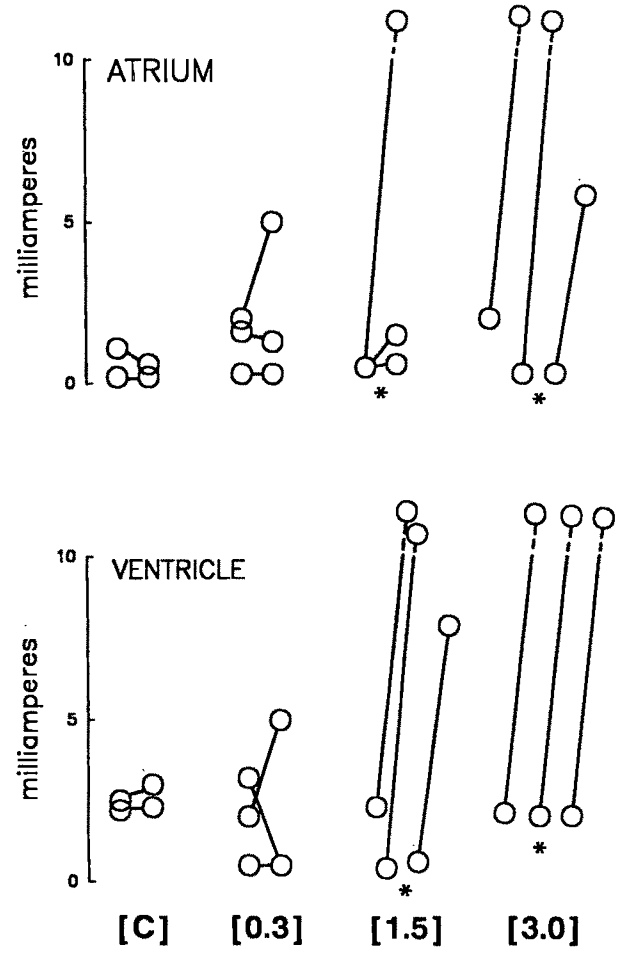


Figure 3. Pacing thresholds before and after bupivacaine. *Significant at the 0.05 level.

the retrograde direction a significant increase occurred at 0.3 μg/mL.

Response to Premature Pacing

No change occurred at 0 μg/mL (Table 3). Because of changes in thresholds and conduction mentioned above, no values could be obtained at 1.5 and 3.0 μg/mL. At 0.3 μg/mL the effective and functional refractory periods of the atrium and ventricle consistently increased slightly (between 6% and 18%). No such change was noted for refractory periods at the AV junction.

Additional Data

No spontaneous tachyarrhythmia occurred or could be induced (including ventricular fibrillation). Spontaneous AV block occurred in two hearts: in one case at 3.0 μg/mL, complete block with a slow escape rhythm showing wide QRS configuration; in another at 1.5 μg/mL, second-degree type I block was followed by 2:1 block with a narrow QRS identical to

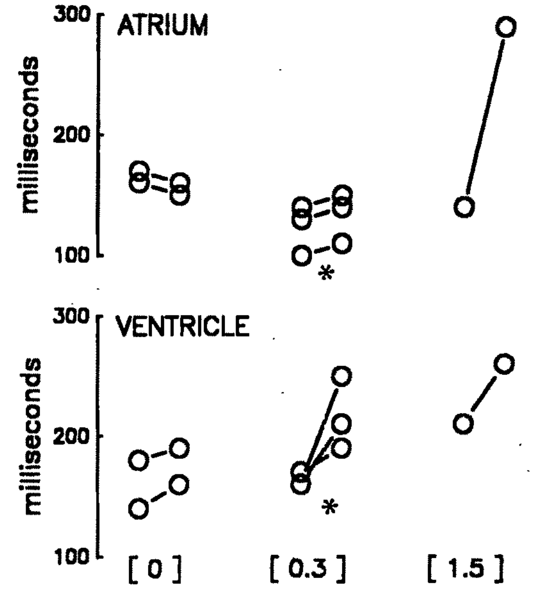


Figure 4. Minimum captured 1:1 cycle before and after bupivacaine. *Significant at the 0.05 level.

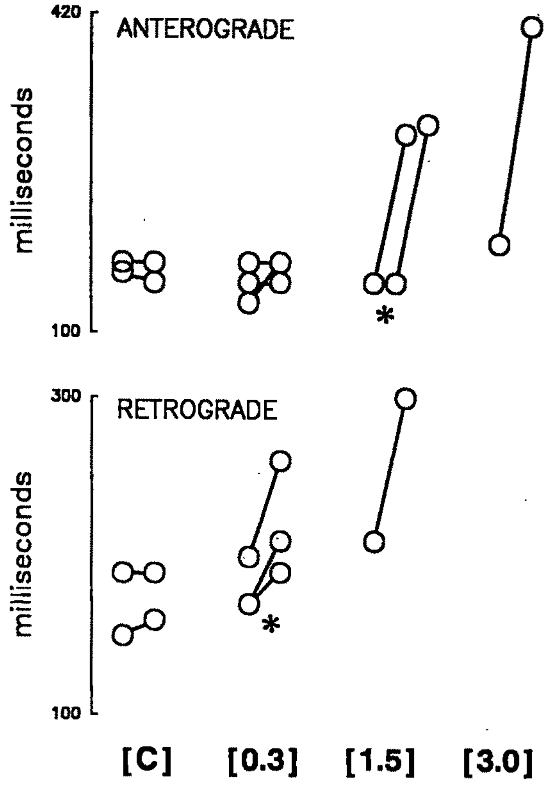


Figure 5. Wenckebach cycle before and after bupivacaine. *Significant at the 0.05 level.

Table 3. Refractory Periods[a]

	[0]				[0.3]						[1.5]						[3.0]					
	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B
A ERP	90	110	80	90	80	85	110	120	90	110	100	200	90	—	100	—	120	—	100	—	110	240
A FRP	110	120	110	115	110	130	140	160	110	130	130	240	110	—	130	—	140	—	155	—	120	280
V ERP	150	150	190	200	180	190	190	220	160	190	210	—	220	—	190	—	150	—	230	—	150	—
V FRP	180	185	210	210	200	210	210	240	185	215	225	—	230	—	210	—	180	—	250	—	170	—
AV ERP ANT	110	120	160	160	110	170	140	160	135	130	130	—	140	—	130	—	140	—	185	—	175	—
AV FRP ANT	190	220	215	220	215	215	215	215	200	210	205	—	200	—	190	—	210	—	235	—	210	—
AV ERP RET	180	185	210	210	200	210	210	—	190	215	225	—	230	—	210	—	180	—	250	—	170	—
AV FRP RET	210	205	235	340	215	230	230	—	220	230	240	—	245	—	220	—	220	—	270	—	225	—

A, atrium; V, ventricle; AV, atrioventricular junction; ERP, effective refractory period; FRP, functional refractory period; ANT, anterograde; RET, retrograde.

[a] Data from each individual heart before and after bupivacaine administration. All values are expressed in milliseconds.

baseline. In this last case, however, during Wenckebach periodicity the alternation of short and long RR intervals resulted in occasional widening of the QRS; two distinct morphologies were present, resembling right and left bundle branch block (this diagnosis cannot be made with certainty in the isolated heart's "standard" ECG). The concentration of 3.0 μg/mL caused marked widening of the QRS, loss of P waves, gradual bradycardia, and asystole in three of three animals after about 20 min of administration. (This unstable state had little effect on the results because almost no stimulation data were obtained in these preparations; values during sinus rhythm were all measured after 5 min of drug administration.)

Discussion

Our understanding of bupivacaine's arrhythmogenicity is only partial: in fact, although the drug's toxicity is widely recognized, we lack a precise definition of what can be considered a "bupivacaine-induced" arrhythmia. Polymorphic ventricular tachycardia (7,9) and a high degree AV block (3,4,17) appear to be more frequent abnormalities, but a ventricular arrhythmia similar to "torsade de pointe" (19) has been reported, as well as nonspecific findings such as premature ventricular contractions (1,2) and QRS widening (1,3,4). The role of bupivacaine in the sequence of events leading to these disturbances is unclear; because the drug depresses myocardial contractility, the resulting hemodynamic changes can affect myocardial perfusion, acid-base balance, oxygen transport, and autonomic tone. All these factors may be implicated in the genesis of arrhythmias.

Our results with the isolated heart confirm that bupivacaine is indeed capable of altering cardiac electrophysiology directly (14). These data may be interpreted in many ways. We adhere to the concepts of automaticity and reentry as they are generally applied in clinical electrophysiology.

Automaticity was unchanged by bupivacaine; this is evidenced by its lack of effect on the spontaneous sinus rate and sinus node recovery time. Our results differ from those of Bosjnak et al. (20). However, these authors studied isolated nodal tissue subject to hypoxia and acidosis, and they noted that adult nodes were less sensitive to bupivacaine than neonatal nodes. No ectopic foci were manifest. The behavior of escape foci seen when AV block was present is difficult to assess (for lack of reference), but their absence during 2:1 block and their spontaneous rate of about one-third to one-half the sinus rate when present, with a wide QRS morphology, roughly parallel the response of other mammalian hearts and, in our view, offer no evidence of a significant change in either normal or abnormal automaticity.

On the other hand, bupivacaine markedly impaired conduction of the electrical impulse. In the working myocardium (atrium and ventricle) this was reflected by increase in the duration of the P wave, QRS complex, QT and AA interval on the resting ECG, the markedly increased pacing thresholds, less efficient 1:1 pacing, and increased refractory periods. In the specialized conduction system, we observed parallel ECG changes (increased PR and AV intervals) as well as an increased point of Wenckebach and, at high doses, spontaneous AV block. We did not record the His potential and therefore cannot offer a description of these effects as "supra or infra His"; however, although the magnitude of ECG changed, the typically decremental nature of the depressed conduction and the type I second-degree block (21) observed after bupivacaine strongly suggest a major effect on the AV node. There was some evidence of His Purkinje involvement (8) (spontaneous or induced aberrant QRS complexes after bupivacaine, not present at baseline). Sinoatrial conduction time was not changed, but this measurement is not a very accurate one as changes of as much as 50% would only translate to 10 ms or less.

Thus, we found that bupivacaine can be responsible for a major depression of conduction (probably dose-related), and it appears that this depression affects the different cardiac structures in heterogeneous fashion (e.g., magnitude of PR and AV interval compared to P wave and QRS complex in sinus rhythm). Depression of conduction and dispersion of refractoriness are well known as prerequisites for reentry (22), and we conclude that this is the mechanism involved in bupivacaine-induced tachyarrhythmias. Reentrant tachyarrhythmias can usually be induced by stimulation (18), although none was induced in our study. However, the induction of arrhythmia also requires an anatomic substrate in the form of scar tissue, in which conduction is already impaired; in normal "homogenous" hearts reentry usually is disorganized, i.e., polymorphic or fibrillatory. This type of reentry requires a "critical mass" of myocardium, and small hearts do not in fact sustain reentry easily (23). Therefore, we did not expect to find these phenomena in the small, healthy hearts we used.

Bupivacaine blocks the fast sodium channels (24–27), the slow calcium channel (25,28–30), and the potassium channels (31). It binds to receptors common to quinidine (24), in a "fast-in, slow-out" fashion, subject to use-dependence (24–27); thus, from a cellular point of view, the drug is remarkably similar to class I antiarrhythmics (Vaughn-Williams classification) especially those of subclass Ia and Ic (32). We found that this similarity holds when examining the electrophysiologic variables of the whole heart. Bupivacaine, like other class I drugs, has no significant effects on sinus node automaticity but does have increased refractory periods of atrial and ventricular myocardium (32) as well as pacing thresholds and impaired conduction at all levels of the conducting system. These effects are all consistent with blockade of the sodium channels; the predominance of impairment of conduction at the AV junction has been reported previously (33) and could be related to the calcium channel blockade, although it can be seen with sodium channel blockers as well, again especially subclass Ia and Ic (32).

The ECG tracing was also affected by bupivacaine in a fashion similar to that observed with other sodium channel blockers (32). Thus we believe that arrhythmias associated with bupivacaine overdose, namely QRS widening, variable degree AV block, premature ventricular contraction, and polymorphic ventricular tachycardias (including possibly torsades de pointe), are mediated by the same mechanisms and are of similar nature to the arrhythmias encountered with class Ia and Ic antiarrhythmic drugs. The treatment of class Ia and Ic antiarrhythmic drug intoxication could be of use in the setting of bupivacaine toxicity.

References

1. De Jong RH, Ronfeld RA, De Rosa RA. Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 1982;61:3–9.
2. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesth Analg 1982;61:317–22.
3. Kotelko DM, Shnider SM, Dailey PA, et al. Bupivacaine induced cardiac arrhythmias in sheep. Anesthesiology 1984;60: 10–8.
4. Rosen MA, Thigpen JW, Shnider SM, Foutz SE, Levinson G, Koike M. Bupivacaine induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 1985;64:1089–96.
5. Chadwick HS. Toxicity and resuscitation in lidocaine or bupivacaine-infused cats. Anesthesiology 1985;63:385–90.
6. Morishima HO, Pedersen H, Finster M, et al. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63:134–9.
7. Kasten GW, Martin ST. Successful cardiovascular resuscitation after massive intravenous bupivacaine overdose in anesthetized dogs. Anesth Analg 1985;64:491–7.
8. Nathy S, Haggmark S, Johansson G, Reiz S. Differential depressant and electrophysiologic cardiotoxicity of local anesthetics. Anesth Analg 1986;65:1263–70.
9. Kasten GW, Martin ST. Comparison of resuscitation of sheep and dogs after bupivacaine induced cardiovascular collapse. Anesth Analg 1986;65:1029–32.
10. Thomas RD, Behbehani MM, Coyle DE, Denson DD. Cardiovascular toxicity of local anesthetics: an alternative hypothesis. Anesth Analg 1986;65:444–50.
11. Kasten GW, Martin ST. Resuscitation from bupivacaine induced cardiovascular toxicity during partial inferior vena cava occlusion. Anesth Analg 1986;65:341–4.
12. Leone BJ, Lehot JJ, Runeiman WB, et al. Effects of lidocaine and bupivacaine on regional myocardial function and coronary blood flow in anesthetized dogs. Br J Anaesth 1988;60:671–9.
13. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine and ropivacaine in sheep. Anesth Analg 1989;69:291–9.
14. Lena SS, Rosen MR. Electrophysiologic effects of bupivacaine on adult, neonatal and fetal guinea pig papillary muscle. Anesthesiology 1989;71:A654.
15. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–7.
16. Marx GF. Cardiotoxicity of local anesthetics—the plot thickens. Anesthesiology 1984;60:3–5.

17. Tanz RD, Heskett T, Loehning RW, Fairfax CA. Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated perfused mammalian heart. Anesth Analg 1984;63:549–56.
18. Josephson ME, Seides SF. Clinical cardiac electrophysiology. Philadelphia: Lea & Febiger, 1979:40–4.
19. Kasten GW, Martin ST. Bupivacaine cardiovascular toxicity: comparison of treatment with bretylium and lidocaine. Anesth Analg 1985;64:911–5.
20. Bosjnak ZW, Stowe DF, Kampine JP. Comparison of lidocaine and bupivacaine depression of sinoatrial nodal activity during hypoxia and acidosis in adult and neonatal guinea pigs. Anesth Analg 1986;65:911–7.
21. Zipes DP, Mendez C, Moe G. Some examples of Wenckebach periodicity in cardiac tissues with an appraisal of mechanisms. In: Rosenbaum MB, Elizari MV, eds. Frontiers of cardiac electrophysiology. Martin Nishoff, 1983.
22. Wit AL. Cardiac arrhythmias: electrophysiologic mechanisms. In: Reiser HJ, Horowitz LN, eds. Mechanisms and treatment of cardiac arrhythmias—relevance of basic studies to clinical management. Baltimore, Munich: Urban and Swartzenberg, 1985:11–37.
23. Allessie MA, Lammers W, Bonke F, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, eds. Cardiac electrophysiology and arrhythmias. Grune & Stratton, 1985:265–75.
24. Clarkson CW, Hondeghem LM. Evidence for a specific receptor site for lidocaine, quinidine and bupivacaine associated with cardiac sodium channels in guinea pig ventricular myocardium. Circ Res 1985;56:496–506.
25. Lynch C. Depression of myocardial contractility in vitro by bupivacaine, etidocaine and lidocaine. Anesth Analg 1986;65: 551–9.
26. Clarkson CW, Follmer CH, Ten Eick RE, Hondeghem LM, Yeh JZ. Evidence for two components of sodium channel block by lidocaine in isolated cardiac myocytes. Circ Res 1988;63:869–78.
27. Arlock P. Actions of three local anesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (V max). Pharmacol Toxicol 1988;63:96–104.
28. Coyle DE, Sperelakis N. Bupivacaine and lidocaine blockage of calcium mediated slow action potentials in guinea pig ventricular muscle. J Pharmacol Exp Ther 1986;242:1001–5.
29. Sanchez-Chapula J. Effects of bupivacaine on membrane currents of guinea pig ventricular myocytes. Eur J Pharmacol 1988;156:303–8.
30. Moller RA, Covino BG. Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 1988;67:107–14.
31. Courtney KR, Kendig JJ. Bupivacaine is an effective potassium channel blocker in heart. Biochim Biophys 1988;939:163–6.
32. Singh BN. Comparative mechanisms of action of artiarrhythmic agents: significance of lengthening repolarization. In: Singh BN, ed. Control of cardiac arrhythmias by lengthening repolarization. Futura Publishing, 1988:53–127.
33. Hotvedt R, Refsum H, Helgesen KG. Cardiac electrophysiologic and hemodynamic effects related to plasma levels of bupivacaine in the dogs. Anesth Analg 1985;64:388–94.

Isoproterenol Corrects the Effects of Bupivacaine on the Electrophysiologic Properties of the Isolated Rabbit Heart

Pierre Lacombe, MD, Gilbert Blaise, MD, Charleen Hollmann, RN, Mario Tanguay, BPharm, and Didier Loulmet, MD

LACOMBE P, BLAISE G, HOLLMANN C, TANGUAY M, LOULMET D. Isoproterenol corrects the effects of bupivacaine on the electrophysiologic properties of the isolated rabbit heart. Anesth Analg 1991;72:70–4.

The purpose of this study was to test the hypothesis that isoproterenol could reverse bupivacaine toxicity. In eight isolated rabbit hearts an electrophysiologic evaluation was performed then repeated during infusion of bupivacaine (1 μg/mL) alone and bupivacaine plus isoproterenol (1–2 μg/mL). Bupivacaine alone increased electrocardiographic intervals (P wave, QRS complex, PR, AV, and QTc interval) and refractory periods of the myocardium and atrioventricular junction as well as the Wenckebach cycle and pacing thresholds. The addition of isoproterenol corrected partially or completely all bupivacaine-induced abnormalities, and decreased sinus cycle length, suggesting a potential therapeutic value in the treatment of bupivacaine intoxication.

Key Words: ANESTHETICS, LOCAL—bupivacaine, cardiac toxicity. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—isoproterenol. HEART, ELECTROPHYSIOLOGY—bupivacaine effects.

Bupivacaine is a commonly used local anesthetic agent. High blood levels in humans have been associated with major disturbances of cardiac rhythm; accidental deaths have been reported (1,2). Drug-induced arrhythmias also occur in experimental animal models (3–16); previous data from our laboratory suggest that these arrhythmias are the result of the drug's major depressant effect on the conduction of electrical impulses at various levels in the heart rather than of changes in cardiac automaticity. In the present study we tested the hypothesis that isoproterenol, a catecholamine with predominant β-adrenergic properties known to facilitate conduction, might antagonize the toxic effects of bupivacaine.

Methods

The hearts of eight rabbits were surgically removed under general anesthesia and mounted on a Langendorff perfusion apparatus. The perfusion solution (119 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2 \cdot 2H_2O$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4 \cdot 7H_2O$, 25 mM $NaHCO_3$, 15 mM glucose) was administered through a cannula attached to the ascending aorta of the isolated heart at a pressure of 85 cm H_2O and a temperature of 37°C.

Paired electrodes (Grass, Quincy, Mass.) were implanted 5 mm apart on the epicardial aspect of each of the four heart chambers to record local electrical activity; a 6F quadripolar ring-electrode catheter was inserted into the superior vena cava and positioned at the level of the atrioventricular junction. A "surface" electrocardiogram was obtained by connecting the right and left "arm" electrodes of a standard electrocardiogram recorder to wet gauze wrapped around the heart—the "leg" electrodes were grounded. All signals were continuously monitored on a multichannel oscilloscope (E for M, VR-6, Honeywell) and recorded on paper at a speed of 50–100 mm/s. Proper positioning of the electrodes was confirmed by examining the amplitude, morphology, and sequence of activation of the electrograms during normal sinus rhythm (Figure 1).

Electrophysiologic variables were obtained by cardiac stimulation using a programmable stimulator (Bloom) delivering rectangular impulses of 1-ms duration at an amplitude twice the diastolic pacing

---

Received from the Departments of Cardiology, Anesthesiology, and Cardiovascular Surgery, Notre-Dame Hospital, University of Montreal, Montreal, Quebec, Canada. Accepted for publication August 24, 1990.

Address correspondence to Dr. Blaise, Department of Anesthesiology, Notre Dame Hospital, 1560 Sherbrooke East, Montreal, Quebec, H2L 4M1.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

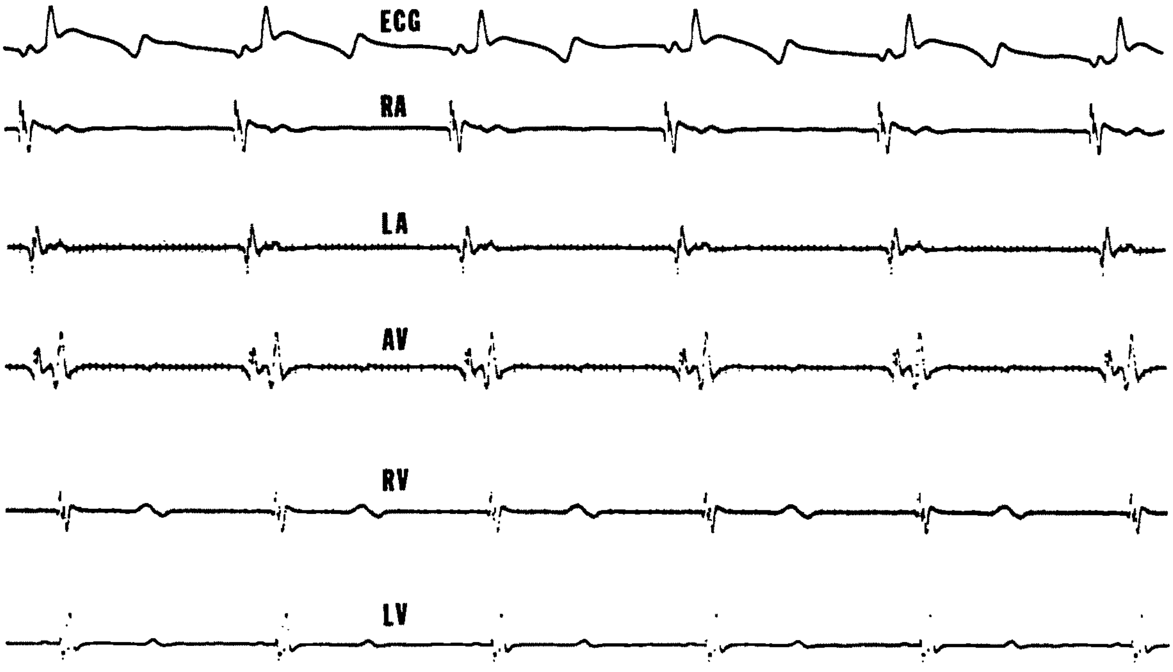


Figure 1. Recordings in sinus rhythm. ECG, electrocardiogram; RA, right atrium; LA, left atrium; AV, atrioventricular junction; RV, right ventricle; LV, left ventricle.

threshold (to a maximum of 10 mA) to the epicardial electrodes on the right atrium and left ventricle. Rapid pacing consisted of successive trains of impulses for 30–60 s at a cycle length initially of 300 ms, decreased by 10–20 ms in each successive sequence until constant capture of the paced chamber could no longer be achieved. Premature pacing was done by delivering successive trains of eight impulses at a constant cycle length of 250 ms, all followed by one premature impulse at an interval of 240 ms. This interval was decreased by 10 ms in each successive sequence until the premature stimulus failed to capture the paced chamber.

The following were measured: (a) spontaneous sinus cycle length, duration of the P wave, QRS complex, PR, QT, and QTc intervals ($QTc = QT/\sqrt{RR}$), as well as the interval between the atrial and ventricular deflections on the intracardiac recording (AV interval); (b) pacing thresholds of the atrium and ventricle; (c) the shortest-paced cycle length achieved at the atrial and ventricular level (shortest 1:1 cycle); (d) the longest-paced cycle length where the paced atrial or ventricular impulses were not all conducted through the atrioventricular junction to the nonpaced chamber (anterograde and retrograde Wenckebach cycle); (e) corrected sinus node recovery time: the time between the spontaneous sinus cycle length and the time to reappearance of sinus rhythm after 60 s of atrial pacing at a cycle of 250 ms; (f) atrial and ventricular refractory periods: the longest premature interval where the premature stimulus failed to capture the paced chamber (basic drive cycle 250 ms except for rabbit 4 at 300 ms); and (g) refractory period of the atrioventricular junction: the interval of prematurity achieved at the atrial or ventricular level where the premature paced impulse did not conduct through the atrioventricular junction to the nonpaced chamber in the anterograde or retrograde direction.

All variables were measured in the basal state, during perfusion with bupivacaine (1 μg/mL) and during perfusion with both bupivacaine (same rate) and isoproterenol (1–2 μg/mL). All measurements were already made after at least 10 min of stabilization (basal state) or drug perfusion. Statistical analysis was done using the one-way analysis of variance with Tukey's multiple-comparison test.

Results

Measurements During Sinus Rhythm

Bupivacaine significantly increased the duration of the P wave (30% increase), PR interval (43% increase), AV interval (45%), QRS complex (45%), and the QTc interval (13%). After the addition of isoproterenol, all values decreased to levels not significantly different from base-

Table 1. Electrophysiologic Data (Data From Each Individual Heart)

	CSNRT			Atrial ERP			Ventricular ERP			Anterograde AVP-ERP			Retrograde AVJ-ERP		
	C	B	B+I	C	B	B+I	C	B	B+I	C	B	B+I	C	B	B+I
1	30	60	—	140	180	140	200	190	140	150	200	150	215	195	150
2	0	70	40	140	140	120	190	200	150	155	160	130	200	215	180
3	40	60	30	140	160	160	180	220	170	155	270	170	195	280	190
4	80	20	—	110	130	110	170	190	190	125	250	130	180	240	205
5	20	70	30	130	—	140	180	—	160	150	—	150	195	—	170
6	45	20	50	80	—	130	190	—	180	110	—	170	195	—	205
7	40	65	40	90	180	90	160	300	160	110	240	130	170	300	200
8	—	—	—	80	140	90	190	—	170	105	330	120	210	—	190
Mean	36.43	52.14	38	113.75	155	122.50	182.5	220	165	132.5	241.67	143.75	195	246	186.25
SD	24.62	22.33	8.37	27.22	21.68	24.93	12.82	46.37	16.04	22.2	58.45	19.23	14.64	43.79	19.04
	NS		NS	^{a}		^{a}	^{a}		^{b}	^{b}		^{b}	NS		NS
		NS			NS			^{a}			NS			NS	

CSNRT, corrected sinus node recovery time; ERP, effective refractory period; AVP, AVJ, atrioventricular junction; C, control value; B, bupivacaine; B+I, bupivacaine and isoproterenol; NS, not significant.

All values are expressed in milliseconds.

[a] Significant at the 0.05 level.

[b] Significant at the 0.01 level.

line (except the PR interval, which was only partially corrected). (See Table 1 and Figure 2.)

Sinus Node Automaticity

Small increases in sinus cycle length (i.e., rate decrease) and corrected sinus node recovery time occurred after bupivacaine, but these changes were inconsistent and not statistically significant. Isoproterenol did, however, decrease sinus cycle length by 18% below baseline ($P < 0.05$) (Figure 2).

Atrioventricular Conduction

The Wenckebach cycle was significantly increased by bupivacaine, both in the anterograde (61%) and retrograde (38%) direction. After adding isoproterenol, mean values were equal to (anterograde) or slightly below (retrograde, 9% decrease) baseline, indicating restoration of normal or even slightly supranormal conduction (Figure 3).

The anterograde atrioventricular junction refractory period also increased after bupivacaine (45%) and reverted to baseline after adding isoproterenol; similar but not statistically significant changes occurred in the retrograde direction.

Effective refractory periods of the atrium and ventricle were increased significantly by bupivacaine but equal to (atrium) or lower (ventricle) than control after the addition of isoproterenol.

Pacing Thresholds

Mean ventricular threshold was significantly increased by 270% by bupivacaine but was comparable to baseline after adding isoproterenol (Figure 4). Atrial thresholds were increased 458% after bupivacaine and remained increased by (210%) after isoproterenol, but these changes did not attain statistical significance.

No spontaneous or pacing-induced tachyarrhythmia occurred with either drug (except for the sinus tachycardia described above after isoproterenol).

Discussion

The results confirmed our previous findings on the mechanisms of bupivacaine toxicity (17): we observed a depression of conduction in the working myocardium (both atrial and ventricular) as well as in the specialized conduction system, but no significant effect on normal automaticity. These properties are common to most local anesthetics that depress the fast sodium response of electrophysiologically active cells (18), class I in the Vaughn-Williams classification.

The clinical and experimental arrhythmias observed in the setting of bupivacaine toxicity are not well defined. The most commonly reported abnormalities are atrioventricular block, ventricular tachycardia (sometimes resembling torsades de pointe), and ventricular fibrillation. These abnormalities are similar to those induced by class I antiarrhythmic

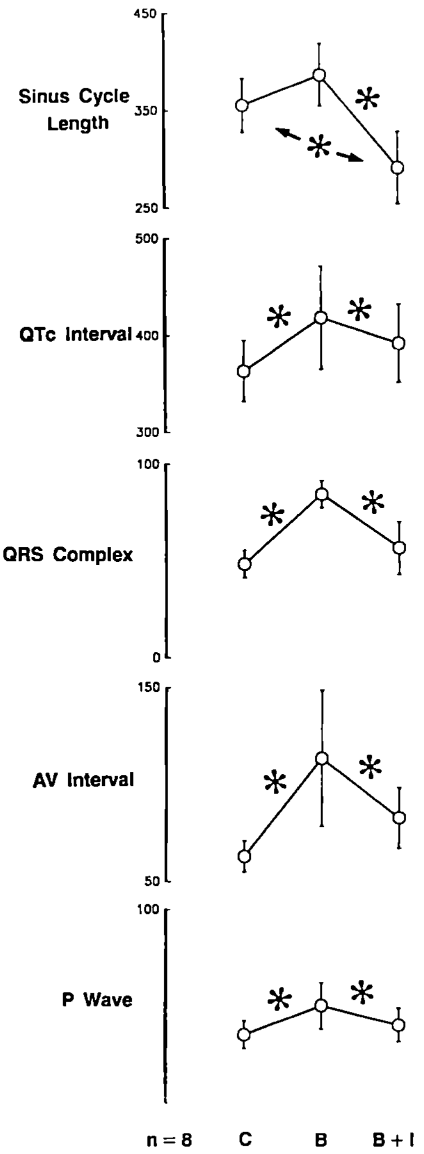


Figure 2. Electrocardiographic intervals. All values are expressed in milliseconds. C, control values; B, bupivacaine; B+I, bupivacaine and isoproterenol. This figure shows the correction by isoproterenol of bupivacaine's effect. Data shown are mean values ± SD with $n = 8$. *Significant at the 0.05 level.

agents; depression of conduction and lengthening of repolarization have been implicated as major mechanisms. The catecholamine isoproterenol facilitates conduction and has been used successfully to treat some of these class I induced arrhythmias.

Although major arrhythmias did not occur at the moderately high dose of bupivacaine we used, in our study the predisposing electrophysiologic abnormalities were present and were corrected by isoproterenol at all levels of myocardial tissue. This effect of isoproterenol was observed in spite of the continued administration of bupivacaine, suggesting different

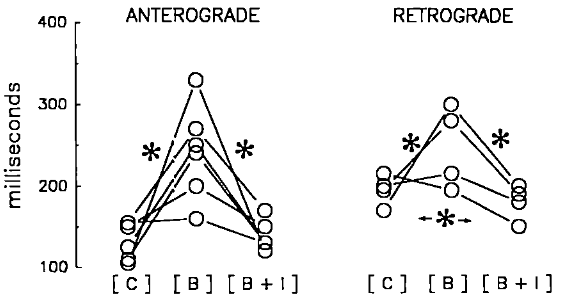


Figure 3. Wenckebach cycle. C, control value; B, bupivacaine; B+I, bupivacaine and isoproterenol. This figure shows variations of the Wenckebach cycle length in all animals in which this value could be determined in the basal state, as well as during the infusions of bupivacaine and isoproterenol. *Significant at the 0.05 level.

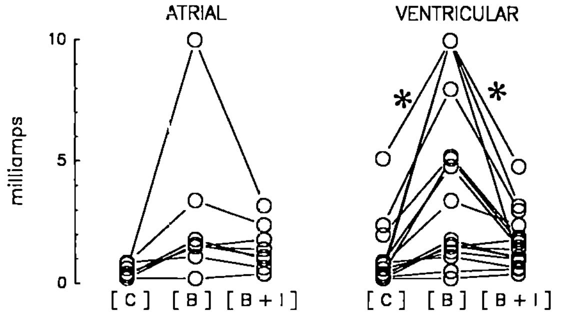


Figure 4. Pacing thresholds. C, control value; B, bupivacaine; B+I, bupivacaine and isoproterenol. This figure shows the effects on pacing thresholds of bupivacaine and correction with isoproterenol. Individual data are given. *Significant at the 0.05 level.

cellular sites of action of the two drugs. The dose of isoproterenol used increased sinus rate by a mean of 22% (maximal increase 35%), a situation comparable to what is seen when isoproterenol is used in clinical practice or during human electrophysiologic studies (19).

At this increased rate, the use-dependent blockade of fast sodium channels by bupivacaine should be of greater magnitude (20), as a result of its "fast-in, slow-out" mode of action on sodium channels. These channels go through three stages: activated, inactivated, and resting; isoproterenol increases heart rate and thus decreases the amount of time spent in the resting state and, consequently, the release of the drug from its binding sites (21,22). Isoproterenol, however, by promoting formation of intracellular cyclic adenosine monophosphate and the subsequent activation of cyclic adenosine monophosphate-dependent phosphorylases, allows the calcium channels to be opened in greater numbers or for a longer period of time (23), thus "replacing" in part the blocked sodium channels. Calcium-dependent action potentials may be produced in cells normally dependent on fast sodium channels inactivated by tetrodotoxin by increasing the extracellular catecholamine concentration (23,24). Thus, isoproterenol could exert its actions by opposing either the calcium channel blocking effect of bupivacaine (25,26) or its sodium blocking effects, both of which appear to be involved in the genesis of arrhythmias.

Attempts to treat bupivacaine toxicity have not met with much success (7,9,11); cardiovascular support (mainly with adrenergic stimulation) is recommended as the most effective therapy. Our results suggest that an important aspect of treatment is the correction of cardiac electrical instability, which is not dependent on metabolic or perfusion changes but directly caused by the drugs; the ability of isoproterenol to correct effectively these abnormalities in vivo and its potential therapeutic uses warrant further study.

References

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–7.
2. Marx GF. Cardiotoxicity of local anesthetics—the plot thickens. Anesthesiology 1984;60:3–5.
3. De Jong RH, Ronfeld RA, de Rosa RA. Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 1982;61:3–9.
4. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesth Analg 1982;61:317–22.
5. Kotelko DM, Shnider SM, Dailey PA, et al. Bupivacaine induced cardiac arrhythmias in sheep. Anesthesiology 1984;60:10–8.
6. Rosen MA, Thigpen JW, Shnider SM, Foutz SE, Levinson G, Koike M. Bupivacaine induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 1985;64:1089–96.
7. Chadwick HS. Toxicity and resuscitation in lidocaine or bupivacaine-infused cats. Anesthesiology 1985;63:385–90.
8. Morishima HO, Pedersen H, Finster M, et al. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63:134–9.
9. Kasten GW, Martin ST. Successful cardiovascular resuscitation after massive intravenous bupivacaine overdose in anesthetized dogs. Anesth Analg 1985;64:491–7.
10. Nathy S, Haggmark S, Johansson G, Reiz S. Differential depressant and electrophysiologic cardiotoxicity of local anesthetics. Anesth Analg 1986;65:1263–70.
11. Kasten GW, Martin ST. Comparison of resuscitation of sheep and dogs after bupivacaine induced cardiovascular collapse. Anesth Analg 1986;65:1029–32.
12. Thomas RD, Behbehani MM, Coyle DE, Denson DD. Cardiovascular toxicity of local anesthetics: an alternative hypothesis. Anesth Analg 1986;65:444–50.
13. Kasten GW, Martin ST. Resuscitation from bupivacaine induced cardiovascular toxicity during partial inferior vena cava occlusion. Anesth Analg 1986;65:341–4.
14. Leone BJ, Lehot JJ, Runeiman WB, et al. Effects of lignocaine and bupivacaine on regional myocardial function and coronary blood flow in anesthetized dogs. Br J Anaesth 1988;60:671–9.
15. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine and ropivacaine in sheep. Anesth Analg 1989;69:291–9.
16. Lena SS, Rosen MR. Electrophysiologic effects of bupivacaine on adult, neonatal and fetal guinea pig papillary muscle. Anesthesiology 1989;71:A654.
17. Lacombe P, Blaise G, Loulmet D, Hollmann C. Electrophysiologic effects of bupivacaine in the isolated rabbit heart. Anesth Analg 1991;72:62–9.
18. Singh BN. Comparative mechanisms of action of artiarrhythmic agents: significance of lengthening repolarization. In: Singh BN, ed. Control of cardiac arrhythmias by lengthening repolarization. Mount Kisco, N.Y.: Futura Publishing, 1988:53–127.
19. Josephson ME, Seides SF. Clinical cardiac electrophysiology. Philadelphia: Lea & Febiger, 1979:40–4.
20. Lynch C. Depression of myocardial contractility in vitro by bupivacaine, etidocaine and lidocaine. Anesth Analg 1986;65:551–9.
21. Clarkson CW, Follmer CH, Ten Eick RE, Hondeghem LM, Yeh JZ. Evidence for two components of sodium channel block by lidocaine in isolated cardiac myocytes. Circ Res 1988;63:869–78.
22. Arlock P. Actions of three local anesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (V max). Pharmacol Toxicol 1988;63:96–104.
23. Green FJ, Watanabe AM. Cellular mechanisms of action of calcium channel antagonists. In: Reiser HJ, Horowitz LN, eds. Mechanisms and treatment of cardiac arrhythmias. Baltimore, Munich: Urban & Swarzenberg, 1989:309–28.
24. Coyle DE, Sperelakis N. Bupivacaine and lidocaine blockage of calcium mediated slow action potentials in guinea pig ventricular muscle. J Pharmacol Exp Ther 1986;242:1001–5.
25. Sanchez-Chapula J. Effects of bupivacaine on membrane currents of guinea pig ventricular myocytes. Eur J Pharmacol 1988;156:303–8.
26. Kasten GW, Martin ST. Bupivacaine cardiovascular toxicity: comparison of treatment with bretylium and lidocaine. Anesth Analg 1985;64:911–5.

Cerebral Effects of Nitrous Oxide When Added to Low and High Concentrations of Isoflurane in the Dog

Ole Kristian Roald, MD, Marianne Forsman, MD, Mona S. Heier, MD, PhD, and Petter A. Steen, MD, PhD

ROALD OK, FORSMAN M, HEIER MS, STEEN PA. Cerebral effects of nitrous oxide when added to low and high concentrations of isoflurane in the dog. Anesth Analg 1991;72:75–9.

The purpose of this canine study was to examine the cerebral vascular and metabolic effects of adding nitrous oxide to isoflurane from 1.4% expired (1 MAC) up to a concentration giving an isoelectric electroencephalogram (EEG). Cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO_2) were determined using a sagittal sinus outflow technique. At 1.4% expired isoflurane, 70% nitrous oxide increased CBF but had no effect on CMRO_2. At 3.1% expired isoflurane, 70% nitrous oxide had no effect on either CBF or CMRO_2. The latter concentration of isoflurane rendered the EEG isoelectric, but when nitrous oxide was added, EEG activity reappeared. To again produce an isoelectric EEG required an increase in the isoflurane concentration to 3.5% ± 0.2% (with no further effect on CMRO_2). The authors also found that at 1.4% isoflurane, 0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of angiotensin significantly decreased CMRO_2 without any effect on CBF. It is concluded that nitrous oxide, when added to isoflurane concentrations ranging from 1.4% to 3.5% in the dog, increases CBF at the low but not the high isoflurane concentrations although it has no effect on CMRO_2.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANESTHETICS, GASES—nitrous oxide. BRAIN, BLOOD FLOW—oxygen consumption.

Isoflurane is associated with dose-related decreases in the cerebral metabolic rate for oxygen (CMRO_2) with a 50% reduction in CMRO_2 being seen when the electroencephalogram (EEG) becomes isoelectric at 2 MAC in the dog (1). This reduction in cerebral metabolic demand might protect the brain during episodes of cerebral ischemia caused by severe hypotension or by regional ischemia during cerebrovascular operation with inadequate collateral cerebral circulation (2). When potent inhalation anesthetics are combined with nitrous oxide, the effect on anesthetic potency defined as MAC (minimal alveolar concentration) appears to be additive (3). If the addition of nitrous oxide to isoflurane renders the EEG isoelectric with a parallel reduction in CMRO_2 at a lower concentration of isoflurane, this could mean a parallel reduction in the concentration of isoflurane required for the same cerebral protective effect.

To our knowledge, only combinations of nitrous oxide with halothane at approximately 1 MAC or below have been studied in the dog (4). The cerebral metabolic effects of adding nitrous oxide to potent inhalation anesthetics above 1 MAC have not been previously reported.

Several studies have reported that the production of deeper levels of anesthesia reduces the increase in cerebral blood flow (CBF) and intracranial pressure caused by nitrous oxide (4–6). It has recently been reported that, in rabbits, the addition of 70% nitrous oxide to 1 MAC isoflurane or halothane results in significantly greater increments in CBF than are observed at 0.5 MAC (7).

We therefore investigated the effects of nitrous oxide on CMRO_2, CBF, and EEG when combined with isoflurane in the dog at concentrations ranging from 1.4% (1 MAC in the dog) to that required to produce an isoelectric EEG.

This work was supported by grants from the Norwegian Research Council for Science and the Humanities and by the Anders Jahres Fund for the Promotion of Science.

Received from the Department of Anesthesiology, Aker Hospital, Oslo; the Institute for Experimental Medical Research, University of Oslo; and the Departments of Anesthesiology and Neurology, Ullevål Hospital, Oslo, Norway. Accepted for publication September 4, 1990.

Address correspondence to Dr. Roald, Department of Anesthesiology, Aker Hospital, 0514 Oslo 5, Norway.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Materials and Methods

The protocol for this study was approved by the National Animal Investigation Committee. Six unmedicated fasting mongrel dogs of either sex weighing 15–20 kg were studied. Anesthesia was induced and maintained throughout the surgical preparation with 1.4% isoflurane in 60%–70% nitrous oxide and oxygen. End-tidal isoflurane was continuously monitored with a multigas monitor (Emma Gambro Engstrøm AB, Stockholm, Sweden). Succinylcholine (2 mg/kg) was given intravenously to facilitate tracheal intubation and thereafter was continuously infused (7.5 $mg \cdot kg^{-1} \cdot h^{-1}$) to maintain muscle paralysis.

Ventilation was controlled with a Harvard animal ventilator with a minute volume sufficient to maintain end tidal Pco_2 close to 5.3 kPa (40 mm Hg), monitored with a capnograph (Eliza, Gambro Engstrøm AB, Stockholm, Sweden). $NaHCO_3$ was administered when necessary to keep the bicarbonate concentration close to 24 mmol/L. Cannulae were inserted into a femoral artery for blood sampling and continuous monitoring of mean arterial blood pressure (MABP) and in a femoral vein for drug and fluid administration. The electrocardiogram was recorded from two upper limb leads. After heparinization (20,000 IU), the sagittal sinus was exposed, isolated, and cannulated as previously described for direct measurement of CBF from anterior, superior, and lateral portions of both hemispheres (equal to approximately 54% of total brain weight) (8,9). The blood flowed passively through a 25-cm extracorporeal loop into the left external jugular vein cannulated with the Seldinger technique (9). Flow from the sagittal sinus was continuously recorded by a flow-through electromagnetic flow probe in this loop (Nycotron 376, Drammen, Norway). After every set of measurements, the calibration was checked by timed collections (9).

A four-lead bifronto-parietal EEG was recorded from screws in the skull. Parietal epidural and esophageal temperatures were monitored with thermistor probes and maintained at 37.0° ± 0.1°C with a heating blanket and a heating lamp as needed. Blood oxygen content was determined from measurement of oxygen tension by electrodes at 37°C (AVL 945, Graz, Austria) and oxyhemoglobin concentration by a spectrophotometric method (10) using 1.34 mL/g as the oxygen carrying capacity of hemoglobin. $CMRo_2$ was calculated as the product of CBF and the arterial-sagittal sinus blood oxygen content difference.

After completion of the surgical procedure and a 30-min stabilization period with 1.4% isoflurane and 70% nitrous oxide, the first set of measurements was taken. Nitrogen was then substituted for nitrous oxide and the second set of measurements was taken after 10 min. In previous canine studies (11,12), we reported nitrous oxide concentrations of less than 5% within 10 min after replacing 70% nitrous oxide with nitrogen in a nonrebreathing system.

A previous study in dogs examining the effects of 1.4%–6% end-expired isoflurane on cerebral metabolism and hemodynamics demonstrated that blood pressure support was necessary at isoflurane concentrations above 3% (1). For this purpose, we selected angiotensin as it is a vasopressor reported to be devoid of effects on regional CBF (13). Before angiotensin was required for blood pressure control in the present study, we wanted to determine if the drug affected CBF or $CMRo_2$ at low isoflurane concentrations. Therefore a continuous infusion of angiotensin (0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was started at 1.4% end-expired isoflurane anesthesia. After 10-min stabilization, a third new set of measurements was taken.

The isoflurane was then increased up to the minimum concentration necessary to render the EEG isoelectric. Angiotensin was infused as needed (Table 1) to maintain MABP above 60 mm Hg. After a stabilization period of 10 min, a fourth set of cerebral and systemic measurements was taken; 70% nitrous oxide was then substituted for nitrogen and a fifth set of measurements was taken.

After substitution of nitrous oxide for nitrogen, the EEG activity reappeared. The isoflurane concentration was therefore further increased until the EEG again became isoelectric. After a sixth set of measurements, the angiotensin infusion was stopped, and the isoflurane concentration was decreased to 2.3%. At this concentration, assuming the MAC of nitrous oxide in the dog is 188%, the dogs were thus exposed to the equivalent of 2 MAC when the 2.3% isoflurane was given with 70% nitrous oxide (3). A seventh set of measurements was taken after 10 min.

All results are expressed as mean value ± the standard error of the mean (SEM). The statistical analysis was two-tailed and based on the analysis of variance model for Latin-squared designed trials with *P* values less than or equal to a level of 5% regarded as statistically significant.

Results

In dogs equilibrated with 1.4% isoflurane anesthesia (1 MAC), the substitution of nitrogen for nitrous oxide decreased CBF significantly but did not change

Table 1. The Cerebral and Systemic Effects of Adding Nitrous Oxide to Isoflurane From 1.4% up to a Concentration Giving an Isoelectric Electroencephalogram

Isoflurane	CBF ($mL \cdot 100\ g^{-1} \cdot min^{-1}$)	$CMRo_2$ ($mL \cdot 100\ g^{-1} \cdot min^{-1}$)	MABP (mm Hg)	Pao_2 (kPa)	$Paco_2$ (kPa)	Angiotensin ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
1.4% + N_2O/O_2	103 ± 15^a	3.66 ± 0.23	96 ± 4	20.0 ± 1.3	5.3 ± 0.1	0
1.4% + N_2/O_2	72 ± 5	3.32 ± 0.21	91 ± 5	19.3 ± 2.8	5.2 ± 0.1	0
1.4% + N_2/O_2	74 ± 5	2.90 ± 0.24^a	137 ± 9^a	19.8 ± 3.0	5.2 ± 0.3	0.9 ± 0.2
3.1% ± 0.1% + N_2/O_2, isoelectric EEG	64 ± 6	2.19 ± 0.14^a	83 ± 13	19.9 ± 2.9	5.3 ± 0.3	1.6 ± 0.3
3.1% ± 0.1% + N_2O/O_2	74 ± 9	2.09 ± 0.16^a	78 ± 13	21.8 ± 1.1	5.9 ± 0.3	3.3 ± 2.0
3.5% ± 0.2% + N_2O/O_2, isoelectric EEG	48 ± 6	2.07 ± 0.09^a	70 ± 14	22.4 ± 1.4	5.4 ± 0.4	4.1 ± 2.1
2.3% + N_2O/O_2	85 ± 9	2.79 ± 0.14^a	101 ± 7	23.8 ± 0.8	5.5 ± 0.2	0

CBF, cerebral blood flow; $CMRo_2$, cerebral metabolic rate for oxygen; MABP, mean arterial blood pressure.
Mean ± SEM for six dogs.
[a] Significantly different from 1.4% isoflurane in N_2/O_2 value with $P < 0.05$.

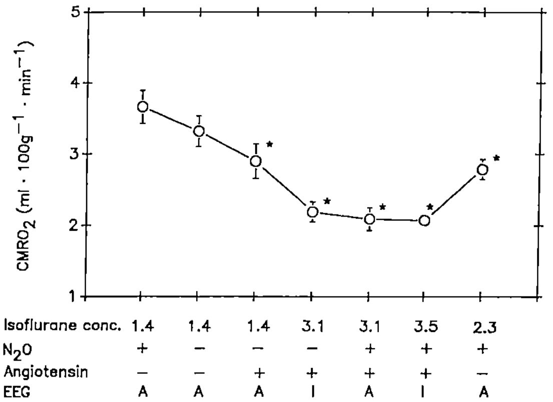


Figure 1. The effect on cerebral oxygen consumption of the addition of nitrous oxide to concentrations of isoflurane from 1.4% to 3.5%. Mean ± SEM for six dogs. Where no error bars are shown, the SEM is less than the size of the symbol. Angiotensin was infused at 1.4% isoflurane concentration and thereafter to support the blood pressure at isoflurane concentrations at and above 3%. *Significantly different from 1.4% isoflurane with and without nitrous oxide. EEG: A = active and I = isoelectric.

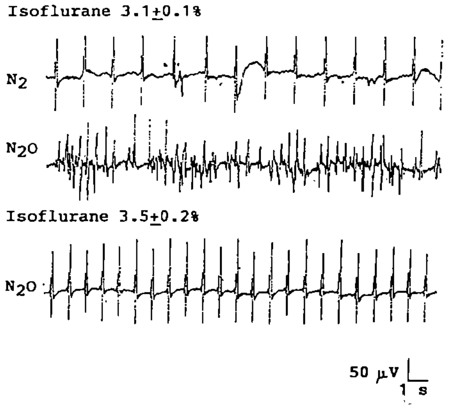


Figure 2. Isoelectric EEG at 3.1% ± 0.1% isoflurane concentrations followed by reappearance of EEG activity after addition of nitrous oxide. Isoelectricity returned when the isoflurane concentration was increased to 3.5% ± 0.2%. The high rhythmic spikes seen are electrocardiographic signals.

$CMRo_2$ (Table 1 and Figure 1). The administration of angiotensin at a mean rate of 0.9 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during 1.4% isoflurane anesthesia decreased $CMRo_2$ significantly by 14% but did not change CBF (Table 1).

When the concentration of isoflurane was increased, the EEGs in all six dogs decreased in frequency and voltage followed by burst suppression and finally isoelectricity at 3.1% ± 0.1% (Figure 2) at which point $CMRo_2$ had decreased further but without significant change in CBF. Substituting nitrous oxide for nitrogen when the concentration of isoflurane was 3.1% ± 0.1% required an increase in the rate of infusion of angiotensin from 1.6 ± 0.3 to 3.3 ± 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to maintain MABP but did not induce any further significant changes in $CMRo_2$ or CBF. On the other hand, electrical activity reappeared in the EEG recordings in all dogs (Figure 2). To again produce electrical silence when nitrous oxide was given with isoflurane required an increase in the isoflurane concentration to 3.5% ± 0.2%. This was not associated with any further significant changes in $CMRo_2$ or CBF, although the angiotensin dose had to be increased to keep MABP above 60 mm Hg.

When the isoflurane concentration was decreased to 2.3% in combination with 70% nitrous oxide, the EEG changed to an irregular slow-activity pattern and the CBF increased to a value numerically intermediate between CBF values associated with 1.4% and 3.1% isoflurane in nitrous oxide but was not significantly different from either. $CMRo_2$ increased to a value between those values obtained at 1.4% and 3.1% isoflurane and this, however, was different from both in statistical significance.

There were no significant changes in arterial blood gas tension or MABP throughout the study except for the increase in MABP when angiotensin was added to the 1.4% concentration of isoflurane (Table 1).

Discussion

The mean values for CBF and $CMRo_2$ at 1.4% and 3.1% ± 0.1% isoflurane concentration without nitrous oxide are in agreement with previous reported results in the dog (1,14). We have previously demonstrated that the experimental dog model used in this study is stable during isoflurane anesthesia administration to the extent that CBF and $CMRo_2$ remained constant over a 3–4-h period (9). Changes in CBF or $CMRo_2$ are, thus, not due to deterioration of the experimental model over time.

The significant increase in CBF with no significant difference in $CMRo_2$ when nitrous oxide instead of nitrogen was combined with 1.4% isoflurane observed in the present study is similar to what has been reported during 0.7%–0.8% halothane anesthesia administration (4). No significant cerebral effects were observed, however, in the present study when nitrous oxide was added to 3.1% ± 0.1% isoflurane anesthesia. Similarly, no significant cerebral effects were reported in previous studies when nitrous oxide was added to 3.0 mg/kg diazepam (11) or 30 mg/kg triazolam anesthesia (12). On the other hand, in awake dogs with total spinal anesthesia (5) or in dogs with minimal (0.2%) halothane anesthesia (4), both CBF and $CMRo_2$ increased significantly when nitrous oxide was added. The latter might be due to the low potency of nitrous oxide in the dog (3) as subanesthetic levels of inhalation anesthetics may induce cerebral excitation (15). These differences in the cerebral effects of nitrous oxide administration might thus be caused by variations in the potency and the quality of the background anesthetic.

The gradual decrease in voltage and frequency in the EEG through burst suppression to isoelectricity with increasing isoflurane concentration from 1.4% to 3.1% is in agreement with the findings of Newberg et al. who reported that the EEG becomes isoelectric in dogs given 3.0% isoflurane (1). The reappearance of the EEG activity after the addition of nitrous oxide to 3.1% isoflurane in the present study was unexpected but is consistent with the apparent EEG activation reported in the rabbit when nitrous oxide is added to 1 MAC of isoflurane anesthesia (7). It is also consistent with the reported central nervous system-mediated increase in splanchnic nerve discharge that occurs when nitrous oxide is added to halothane anesthesia in the cat (16). It is in contrast to the reported slower EEG frequencies seen in humans when nitrous oxide is added to diethyl ether (17) or to 0.8% halothane anesthesia (18). The addition of nitrous oxide to fentanyl anesthesia in the dog has no effect on the EEG activity (19). Such variability thus limits the usefulness of the EEG for determining the depth of anesthesia when nitrous oxide is added to another anesthetic.

The anesthetic effects of combinations of MAC fractions of nitrous oxide and isoflurane are reported to be additive (3,20). The effects on cerebral metabolism and cerebral electrical activity of the same MAC fractions of nitrous oxide and isoflurane, on the other hand, are different (4,14). Thus in the present study $CMRo_2$ during 2.3% isoflurane plus nitrous oxide administration was significantly higher than that obtained with the equivalent MAC value using isoflurane alone (3.1% ± 0.1%). The EEG was also active at 2.3% isoflurane plus nitrous oxide in contrast to an isoelectric EEG at 3.1% ± 0.1% isoflurane alone. That isoflurane (and other inhalation anesthetics) decreases $CMRo_2$ in parallel with a decrease in the cerebral cortical electrical activity is as expected and as previously reported by Newberg et al. (1); however, a drug's anesthetic effects and cerebral metabolic effects need not be directly correlated as pointed out by Richards (21). If the reduction in $CMRo_2$ during isoflurane anesthesia has a potential cerebral protective effect, this is not enhanced by adding nitrous oxide at isoflurane concentrations above 1 MAC, at least in the dog.

Isoflurane anesthesia in the present study was hemodynamically tolerated even at a concentration that produced an isoelectric EEG. When nitrous oxide was added at this latter concentration, the dogs became hemodynamically unstable and the rate of infusion of angiotensin had to be doubled, questioning the safety of adding nitrous oxide to isoflurane in potencies of near 2 MAC (22).

The significant decrease in $CMRo_2$ with angiotensin during 1.4% isoflurane anesthesia seen in the present study is in contrast to the report that in cats angiotensin does not affect $CMRo_2$ during isoflurane anesthesia (23). This discrepancy may be due to a species difference. It could be speculated that the decrease in $CMRo_2$ was due to a facilitation of adrenergic transmission by angiotensin (24), as adrenergic agonists reduce the anesthetic requirement in isoflurane-anesthetized dogs (25).

It is concluded that when nitrous oxide is added to dogs during isoflurane anesthesia in increasing concentrations from 1.4% to 3.5%, the initial cerebral vasodilatory effect of nitrous oxide is abolished while $CMRo_2$ is not affected at either concentration. This suggests that increasing depth of anesthesia decreases any potential intracranial pressure effects of nitrous oxide, whereas nitrous oxide itself offers no metabolic cerebral protective effects beyond whatever protective effects isoflurane may have.

References

1. Newberg LA, Milde JH, Michenfelder JD. The cerebral metabolic effects of isoflurane at and above concentrations that suppress cortical electrical activity. Anesthesiology 1983;59: 23–8.
2. Michenfelder JD, Sundt TM, Fode N, Sharbrough FW. Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischemia during carotid endarterectomy. Anesthesiology 1987;67:336–40.
3. Quasha AL, Eger EI II, Tinker JH. Determination and applications of MAC. Anesthesiology 1980;53:315–34.
4. Theye RA, Michenfelder JD. The effect of nitrous oxide on canine cerebral metabolism. Anesthesiology 1968;29:1119–24.
5. Sakabe T, Kuramoto T, Inoue S, Takeshita H. Cerebral effects of nitrous oxide in the dog. Anesthesiology 1978;48:195–200.
6. Phirman JR, Shapiro HM. Modification of nitrous oxide-induced intracranial hypertension by prior induction of anesthesia. Anesthesiology 1977;46:150–1.
7. Drummond JC, Scheller MS, Todd MM. The effect of nitrous oxide on cortical cerebral blood flow during anesthesia with halothane and isoflurane, with and without morphine, in the rabbit. Anesth Analg 1987;66:1083–9.
8. Michenfelder JD, Messick JM, Theye RA. Simultaneous cerebral blood flow measured by direct and indirect methods. J Surg Res 1968;8:475–81.
9. Roald OK, Forsman M, Steen PA. The effect of prolonged isoflurane anaesthesia on cerebral blood flow and metabolism in the dog. Acta Anaesthesiol Scand 1989;33:210–3.
10. Refsum HE, Sveinsson SL. Spectrophotometric determination of hemoglobin oxygen saturation in hemolyzed whole blood. Scand J Clin Lab Invest 1956;8:67–70.
11. Roald OK, Steen PA, Milde JH, Michenfelder JD. Reversal of the cerebral effects of diazepam in the dog by the benzodiazepine antagonist Ro15-1788. Acta Anaesthesiol Scand 1986;30: 341–5.
12. Roald OK, Steen PA, Stangland K, Michenfelder JD. The effects of triazolam on cerebral blood flow and metabolism in the dog. Acta Anaesthesiol Scand 1986;30:223–6.
13. Olesen J. The effect of intracarotid epinephrine, norepinephrine and angiotensin on the regional cerebral blood flow in man. Neurology 1972;22:978–87.
14. Cucchiara RF, Theye RA, Michenfelder JD. The effects of isoflurane on canine cerebral metabolism and blood flow. Anesthesiology 1974;40:571–4.
15. Winters WD, Forer-Aldo T, Guzman-Florec C, Alcaraz M. The cataleptic state induced by ketamine: a review of the neuropharmacology of anesthesia. Neuropharmacology 1972;11:303–15.
16. Funaka AF, Epstein RM. Sympathetic excitation during nitrous oxide—halothane anesthesia in the cat. Anesthesiology 1973; 39:23–36.
17. Faulconer A Jr. Correlation of concentrations of ether in arterial blood with electroencephalographic patterns occurring during ether-oxygen and during nitrous-oxide, oxygen and ether anaesthesia of human surgical patients. Anesthesiology 1952; 13:361–9.
18. Sakabe T, Kuramoto T, Kumagae S, Takeshita H. Cerebral responses to the addition of nitrous oxide to halothane in man. Br J Anaesth 1976;48:957–62.
19. Sebel PS, Bovil JG, Wauquier A, Rog P. Effect of high-dose fentanyl anaesthesia on the electroencephalogram. Anesthesiology 1981;55:203–11.
20. Hornbein TF, Eger EI II, Winter PM, Smith G, Wetstone D, Smith KH. The minimum alveolar concentration of nitrous oxide in man. Anesth Analg 1982;61:553–6.
21. Richards CD. The mechanisms of general anaesthesia. In: Norman J, Whitwam JG, eds. Topical reviews in anaesthesia. Volume 1. Bristol: John Wright & Sons, 1980:1–85.
22. Nathan HJ. Nitrous oxide worsens myocardial ischemia in isoflurane-anesthetized dogs. Anesthesiology 1988;68:407–15.
23. Todd MM, Drummond JC. A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. Anesthesiology 1984;60:276–82.
24. Zimmerman BG. Actions of angiotensin on adrenergic nerve endings. Fed Proc 1978;37:199–202.
25. Maze M, Vickery RG, Merlone SC, Gaba DM. Anesthetic and hemodynamic effects of the alpha$_2$-adrenergic agonist, aszepexole, in isoflurane-anesthetized dogs. Anesthesiology 1988;68:689–94.

ANESTH ANALG
1991;72:80–3

Effective Doses of Epidural Morphine for Relief of Postcholecystectomy Pain

Hiroshi Yamaguchi, MD, Seiji Watanabe, MD, PhD, Izumi Harukuni, MD,
and Yoshihiro Hamaya, MD

YAMAGUCHI H, WATANABE S, HARUKUNI I, HAMAYA Y. Effective doses of epidural morphine for relief of postcholecystectomy pain. Anesth Analg 1991;72: 80–3.

Having previously established the effective dose of intrathecal morphine for relief of postcholecystectomy pain, we determined in this study the effective dose of epidural morphine for relief of postcholecystectomy pain in 154 patients given epidural injections of a placebo (group 1, n = 49), 2 mg morphine (group 2, n = 54), or 4 mg morphine (group 3, n = 51) intraoperatively mixed in 1.5% lidocaine. The percentage of patients who did not request an analgesic, 30 mg IM pentazocine, for relief of pain during the first 24 postoperative hours was significantly greater in groups 2 and 3 than in group 1. In patients who did need 30 mg IM pentazocine postoperatively, the number of times pentazocine was administered was also significantly greater in group 1 than in groups 2 and 3. The percentage of patients developing respiratory depression or vomiting in the first 48 postoperative hours was similar in the three groups. Based on the present data and those we previously reported for intrathecal morphine, we conclude that an epidural morphine dose of 2–4 mg and an intrathecal morphine dose of 0.06–0.12 mg are equipotent for relief of postcholecystectomy pain.

Key Words: PAIN, POSTOPERATIVE. ANALGESIC, MORPHINE. ANESTHETIC TECHNIQUES, SPINAL AND EPIDURAL—morphine.

Epidural morphine is widely used for postoperative pain relief (1–4), but may be accompanied by side effects such as respiratory depression, vomiting, and pruritus (4–7). Views on the best dose of morphine to use and the incidence of side effects differ, however, from one report to another (2–4,7–9). We previously reported the minimal effective morphine dose with the lowest incidence of side effects when administered intrathecally for pain relief after cholecystectomy (10). From the pharmacokinetic viewpoint, 2%–4% of epidurally administered morphine is available in cerebrospinal fluid (11–13). But what constitutes equipotent doses of intrathecal and epidural morphine for relief of postoperative pain relief has not been determined.

In the present study, we prospectively investigated the analgesic efficacy and the incidence of side effects of epidural morphine doses of 0–4 mg in patients undergoing cholecystectomy and compared them with those of intrathecal morphine doses that we have previously reported (10).

Materials and Methods

We studied 154 patients, ASA physical status I or II, scheduled for elective cholecystectomy for cholelithiasis between October 1984 and December 1987 at the Mito Saiseikai General Hospital. The research protocol was approved by the hospital ethical committee. Patients were assigned preoperatively at random to one of the following groups: group 1 (epidural morphine dose, 0 mg); group 2 (2 mg); or group 3 (4 mg). Patients receiving pre- or intraoperative opiates or other analgesics and/or antiemetics were not included in the study. Written informed consent was obtained from each patient.

All patients were premedicated with 1.0 mg oral flunitrazepam 90 min before entering the operating theater. An epidural catheter was placed at the L2-3 interspace. Epidural anesthesia began with the injection of 15 mL of 1.5% lidocaine solution (with 1:200,000 epinephrine). General anesthesia was then induced with 5 mg/kg IV thiopental followed by

---

Received from the Department of Anesthesia, Mito Saiseikai General Hospital, Mito City, Ibaraki, Japan. Accepted for publication September 6, 1990.

Address correspondence to Dr. Watanabe, Department of Anesthesia, Mito Saiseikai General Hospital, 3-3-10, Futabadai, Mito City, Ibaraki, 311-41, Japan.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

tracheal intubation facilitated by 1 mg/kg IV succinylcholine. Anesthesia was maintained with 0.5%–1.0% enflurane and 67% nitrous oxide in oxygen. About 50 min after the first epidural lidocaine injection, a predetermined dose of morphine hydrochloride mixed in 7 mL of 1.5% lidocaine solution (with 1:200,000 epinephrine) was epidurally injected in groups 2 and 3, but without morphine in group 1. During surgery 7 mL of 1.5% lidocaine solution was administered epidurally every 50 min. No intravenous analgesics were given during surgery. After tracheal extubation, the patients were returned to the ward.

The patients requesting an analgesic for relief of postoperative incisional pain were given 30 mg IM pentazocine. For 48 h after the epidural injection of the lidocaine solution with or without morphine, the following observations and recordings were made for each patient by ward nurses who were not aware of the epidural morphine doses: (a) the time when the first analgesic (pentazocine) was requested and given for relief of incisional pain, regardless of intensity; (b) the number of times pentazocine was administered during the first 24 postoperative hours; (c) heart rate (every 10 min) and respiratory rate (every half hour) using a thoracic impedance detector incorporated in the electrocardiographic electrodes (Life Scope 11; Nihon Kohden, Tokyo, Japan); (d) time and frequency of any vomiting; and (e) whether (and when) patients complained of pruritus. On the first postoperative day each patient was asked whether colicky abdominal pain had occurred. To evaluate respiratory depression, the right radial artery was used for blood samples for $Paco_2$ determination (a) when respiratory rate was less than 10 breaths/min, (b) when a patient failed to respond to verbal commands, and (c) 5–8 h after the epidural injection with or without morphine. When $Paco_2$ was above 50 mm Hg, arterial blood gas analysis was repeated every 2 h for up to 20 h after surgery. The incidence of urinary retention could not be evaluated because urethral catheters were in place during and after surgery.

In patients who never needed an analgesic during the first 24-h period after the epidural lidocaine injection with or without morphine, pain relief was considered effective and labeled as "pain relief." Patients who vomited in the first 48-h period were labeled as "vomiting." Patients with a respiratory rate of 10 breaths/min or less and/or a $Paco_2$ of 50 mm Hg or more on one or more occasions were considered to have experienced respiratory depression and were labeled as "respiratory depression." Those who complained of pruritus were labeled "pruritus." The percentages of pain relief, respiratory depression, vomiting, and pruritus patients, the time between epidural lidocaine injection with or without morphine and the first analgesic given postoperatively, and the number of times analgesics were given in non-"pain relief" patients during the first 24-h period were compared among the three groups. Demographic data were analyzed using analysis of variance, followed by Bonferroni's correction of the *t*-test. The percentages of pain relief, respiratory depression, vomiting, and pruritus patients were analyzed statistically with a χ^2 test and Bonferroni's correction. The number of times analgesics were given to non-pain relief patients was compared among the three groups using a χ^2 test. Values of $P < 0.05$ were considered to be statistically significant.

Table 1. Patient Data (mean ± SD)

	Group		
	1	2	3
n	49	54	51
Male/female	17/32	17/37	19/32
Dose of epidural morphine (mg)	0	2	4
Age (yr)	57 ± 16	58 ± 14	53 ± 14
Height (cm)	165 ± 6	155 ± 10	156 ± 8
Weight (kg)	62 ± 11	57 ± 11	58 ± 8
Duration of surgery (h)	2.3 ± 1.2	2.5 ± 1.0	2.2 ± 1.4

No significant differences among the three groups.

Results

There were no significant differences among the three groups in mean age, height, weight, or duration of surgery (Table 1). Fifteen minutes after the first epidural lidocaine injection, the cephalad level of analgesia obtained was T-4 to T-6 by pinprick.

The percentages of postoperative pain relief were significantly greater in groups 2 (2 mg) and 3 (4 mg) than in group 1 (0 mg) ($P < 0.05$), but there was no statistically significant difference between groups 2 and 3 (Figure 1).

There was a significant difference in the three groups in the number of times pentazocine was administered postoperatively in patients who needed something more than the initial epidural injection of morphine for the relief of postoperative pain (Table 2). Also, the time until pentazocine was first given was significantly shorter in group 1 (2.7 ± 3.1 h) than in group 2 (8.7 ± 6.9 h) or group 3 (8.3 ± 7.3 h), $P < 0.05$. There was no significant difference between groups 2 and 3 in either frequency of administration

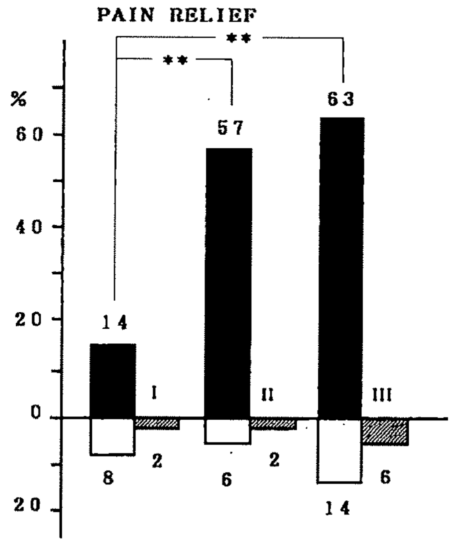


Figure 1. Percentages of patients in whom intraoperative epidural morphine alone eliminated postoperative pain in the three groups of patients (*solid bar*), together with both the percentages of patients who vomited (*open bar*) and the percentages of patients who developed respiratory depression (*hatched bar*). **Significant difference between groups 1 and 2, and between groups 1 and 3, $P < 0.01$.

Table 2. Number of Times 30 mg Intramuscular Pentazocine Was Needed Postoperatively in Patients in Whom Intraoperative Epidural Morphine Alone Was Not Sufficient to Prevent Postoperative Pain

	Group		
	1	2[a]	3[a]
Number of administrations			
1	16	21	18
2	9	2	1
3	11	0	0
4	2	0	0
5	1	0	0
Total	39	23	19

[a] Significant difference between groups 1 and 2, and between groups 1 and 3, $P < 0.05$ versus group 1.

or time until the first administration of pentazocine postoperatively.

Respiratory depression was observed in three patients in group 3 and one patient in group 1, but did not occur in group 2. The three patients in group 3 developed Pa_{CO_2} levels >50 mm Hg (55 mm Hg was the highest level) that lasted 10–14 h, although responses to verbal commands remained normal. Two of the three patients were in the pain relief group, and their respiratory rates were 7 and 9 breaths/min. One patient in group 1 was in the non-pain relief category and needed four injections of pentazocine postoperatively. The incidence of respiratory depression in group 3 was not significantly different from that in groups 1 and 2 (Figure 1).

There were no significant differences in the incidence of vomiting among groups 1, 2, and 3. The four vomiting patients in group 1 required pentazocine, and two of the three vomiting patients in group 2 and five of the seven vomiting patients in group 3 were classified as pain relief.

Three patients, one in group 1 and two in group 3, complained of general pruritus. None of them were the group of patients in whom epidural morphine was considered pain relief.

Postoperative interviews revealed that no patients had colicky abdominal pain during the first 48 h after surgery.

Discussion

There are many reports of epidural morphine administration in the dose range from 2 to 10 mg for postoperative pain relief (1–4). We previously reported that the minimal effective intrathecal morphine dose for pain relief after abdominal hysterectomy or cholecystectomy was 0.04 mg (14) and 0.06 mg (10), respectively, the lowest effective dose that has been reported. The percent efficacy with these lowest doses was about 60% on average, which is the same as that in the present study. The effective dose range of epidural morphine with the lowest incidence of side effects after cholecystectomy was 2–4 mg, but no attempt was made in the present study to determine an upper as well as a lower limit of dose of epidural morphine.

Pharmacokinetically, no more than 2% (11,13) to 4% (12) of morphine epidurally administered is available in cerebrospinal fluid. From the clinical point of view, Chadwick and Ready (15) reported in their retrospective and uncontrolled study that the intrathecal morphine dose necessary for postcesarean pain management is one-sixteenth to one-tenth of the doses required for epidural administration. Our results indicate that 2–4 mg of epidurally administered morphine was effective for relief of postcholecystectomy pain and equipotent to 0.06–0.12 mg of intrathecally administered morphine hydrochloride, which is equivalent to 3% of the epidurally administered dose, an observation in agreement with previous pharmacokinetic data (11–13).

In the present study the incidence of postoperative incisional pain was calculated using the number of patients who requested and were given pentazocine for incisional pain during the first 24 h regardless of intensity (10,14). Fifty-seven percent to 67% efficacy, however, is not adequate from the clinical viewpoint, even though in the category of non-pain relief patients in groups 2 and 3 pentazocine was needed only once or twice in the first 24 h, significantly less often than in group 1.

Previous reports (8,16) have suggested that the larger the epidural morphine dose, the greater the incidence of side effects, although Pybus and Torda (17) observed no significant relationship between epidural morphine doses (2–8 mg) and the incidence of side effects. Side effects such as delayed onset of respiratory depression, nausea, vomiting, urinary retention, and pruritus have often accompanied the lumbar epidural injection of doses of morphine as small as 5 mg (2,3) and the thoracic epidural injection of 2 mg morphine (1). The respiratory depression observed in three patients in the present study in group 3 could be attributed to epidural morphine itself, because two of these three patients fell into the category of those in whom epidural morphine was considered pain relief. The present study failed to determine an upper, as well as a lower, limit dose of lumbar epidural morphine for postcholecystectomy pain relief. In group 3 more patients tended to develop respiratory depression and vomiting than those in group 2. On the basis of intrathecal availability of epidurally administered morphine, we speculate that 4 mg of morphine injected epidurally may be an overdose for some patients in group 3.

Systemic narcotics may precipitate spasm of the sphincter of Oddi. There are no data available about the effect of epidural morphine on the sphincter of Oddi. Olshwang et al. reported no incidence of urethral colic and spasm of the urinary bladder when epidural morphine was administered for relief of urethral colic pain (18). In the present study no patients complained of colicky abdominal pain indicative of either biliary or urethral colic.

In conclusion, 2–4 mg morphine epidurally administered is equipotent with 0.06–0.12 mg morphine administered intrathecally, both in terms of relief of postoperative pain and the incidence of side effects.

We are very grateful to Dr. G. Trahern, SSC Laboratory, Dallas, Texas, for his linguistic help with the manuscript.

References

1. Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. Br J Anaesth 1982;54:479–86.
2. El-Baz NMI, Faber P, Jensik RJ. Continuous epidural infusion of morphine for treatment of pain after thoracic surgery: a new technique. Anesth Analg 1984;63:757–64.
3. Allen PD, Walman T, Consepcion M, et al. Epidural morphine provides postoperative pain relief in peripheral vascular and orthopedic surgical patients: a dose response study. Anesth Analg 1986;65:165–70.
4. Scheinin B, Rosenberg PH. Effect of prophylactic epidural morphine or bupivacaine on postoperative pain after upper abdominal surgery. Acta Anaesthesiol Scand 1982;26:474–8.
5. Madsen JV, Rybro LR, Schurizek BA, Joensen HF, Moller LV, Wernberg M. Respiratory depression following postoperative analgesia with epidural morphine. Acta Anaesthesiol Scand 1986;30:417–20.
6. Etches RC, Sandler AN, Daley MD. Respiratory depression and spinal opioids. Can J Anaesth 1989;36:165–85.
7. Norgberg G. Pharmacokinetic aspects of spinal morphine analgesia. Acta Anaesthesiol Scand 1984;28(S79):6–38.
8. Lanz E, Kehrberger E, Theiss D. Epidural morphine: a clinical double-blind study of dosage. Anesth Analg 1985;64:786–91.
9. Asantila R, Rosenberg PH, Scheinin B. Comparison of different methods of postoperative pain analgesia after thoracotomy. Acta Anaesthesiol Scand 1986;30:421–5.
10. Yamaguchi H, Watanabe S, Motokawa K, Ishizawa Y. Intrathecal morphine dose-response data for pain relief after cholecystectomy. Anesth Analg 1990;70:168–71.
11. Norberg G, Hendner T, Mellstrand T, Borg L. Pharmacokinetics of epidural morphine in man. Eur J Clin Pharmacol 1984;26:233–7.
12. Sjöström S, Hartvig P, Persson P, Tamsen A. Pharmacokinetics of epidural morphine and meperidine in humans. Anesthesiology 1987;67:877–88.
13. Dahlström B, Tamsen A, Paalzow L, Hartvig P. Patient-controlled analgesic therapy. IV. Pharmacokinetics and analgesic plasma concentrations of morphine. Clin Pharmacokinet 1982;7:266–79.
14. Yamaguchi H, Watanabe S, Fukuda T, Takahashi H, Motokawa K, Ishizawa Y. Minimal effective intrathecal morphine dose for pain relief after transabdominal hysterectomy. Anesth Analg 1989;68:537–40.
15. Chadwick HS, Ready LB. Intrathecal and epidural morphine sulfate for postcesarean analgesia—a clinical comparison. Anesthesiology 1988;67:925–9.
16. Martin R, Salbaing J, Blaise G, Tetrault JP, Tetreault L. Epidural morphine for postoperative pain relief: a dose-response curve. Anesthesiology 1982;56:423–6.
17. Pybus DA, Torda TA. Dose-effect relationships of extradural morphine. Br J Anaesth 1982;54:1259–62.
18. Olshwang D, Shapiro A, Perlberg S, Magora F. The effect of epidural morphine on urethral colic and spasm of the bladder. Pain 1984;18:97–101.

ANESTH ANALG
1991;72:84-8

Pretreatment With *d*-Tubocurarine, Vecuronium, and Pancuronium Attenuates Succinylcholine-Induced Increases in Plasma Norepinephrine Concentrations in Humans

Shuzo Oshita, MD, Sadahei Denda, MD, Yoshiki Fujiwara, MD, Hiroshi Takeshita, MD, and Futami Kosaka, MD

OSHITA S, DENDA S, FUJIWARA Y, TAKESHITA H, KOSAKA F. Pretreatment with *d*-tubocurarine, vecuronium, and pancuronium attenuates succinylcholine-induced increases in plasma norepinephrine concentrations in humans. Anesth Analg 1991;72:84–8.

We studied in patients the effect of d-tubocurarine, which has sympathetic ganglion blocking action, on succinylcholine-induced increases in plasma levels of catecholamines, and compared it with the effects of vecuronium and pancuronium, which have little sympathetic ganglion blocking action. Thirty-two patients were divided into five groups: seven were given 3 mL saline; seven received 1 mg/kg succinylcholine; and six, seven, and five patients were given 0.08 mg/kg d-tubocurarine, 0.01 mg/kg vecuronium, and 0.01 mg/kg pancuronium, respectively, all of which were injected 5 min before 1 mg/kg succinylcholine. Succinylcholine alone significantly increased plasma norepinephrine concentrations, systolic blood pressure, and heart rate from 187 ± 39 pg/mL (mean ± SEM), 93 ± 2 mm Hg, and 77 ± 4 beats/min to 429 ± 61 pg/mL, 120 ± 7 mm Hg, and 102 ± 6 beats/min, respectively, with onset of fasciculations. Pretreatment with d-tubocurarine, vecuronium, and pancuronium significantly and equally attenuated both the fasciculations and the cardiovascular responses to succinylcholine. These results suggest that the sympathetic ganglion blocking action of neuromuscular relaxants when given before succinylcholine is not an important factor in attenuation of succinylcholine-induced increases in plasma levels of catecholamines.

Key Words: NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE, *d*-TUBOCURARINE, VECURONIUM, PANCURONIUM. SYMPATHETIC NERVOUS SYSTEM. CATECHOLAMINES.

Alcuronium, administered 5 min before 1 mg/kg intravenous (IV) succinylcholine, attenuates succinylcholine-induced increases in plasma norepinephrine concentrations, systolic blood pressure, and heart rate (1). Although the mechanism by which alcuronium attenuates these cardiovascular effects of succinylcholine is not clear, it has been postulated that alcuronium, which has a sympathetic ganglion blocking action, combines with the nicotinic receptors at the sympathetic ganglia before succinylcholine is administered and blocks the agonistic action of succinylcholine on these receptors (1). If so, similar results would be expected when patients are pretreated with *d*-tubocurarine, which has a slightly greater blocking action than alcuronium on sympathetic ganglia (2), but not with vecuronium or pancuronium, both of which have little sympathetic ganglion blocking action (2). Hence, the present study was designed to evaluate the effects of pretreatment with *d*-tubocurarine, vecuronium, and pancuronium on succinylcholine-induced increases in plasma catecholamine concentrations, systolic blood pressure, and heart rate in patients anesthetized with enflurane.

Methods

The study was performed on 32 patients without symptomatic neuromuscular or cardiovascular disease. All patients were scheduled for major surgical interventions that required invasive cardiovascular monitoring. Our protocol was approved by the Hos-

---

Received from the Department of Anesthesiology-Resuscitology, Yamaguchi University Hospital, Ube, Yamaguchi, Japan; and the Department of Anesthesiology-Resuscitology, Okayama University Hospital, Okayama, Japan. Accepted for publication August 13, 1990.

Address correspondence to Dr. Oshita, Department of Anesthesiology-Resuscitology, Yamaguchi University Hospital, Ube, Yamaguchi 755, Japan.

©1991 by the International Anesthesia Research Society

0003-2999/91/$3.50

pital Committee on Human Study, and written informed consent was obtained from all patients.

The details of the experimental design were similar to those of our previous study (1). The patients were randomly assigned to one of five groups: seven patients received 3 mL IV saline (saline group); seven patients received 1 mg/kg IV succinylcholine (succinylcholine group); six patients received 0.08 mg/kg IV *d*-tubocurarine (*d*-tubocurarine group); seven patients received 0.01 mg/kg IV vecuronium (vecuronium group), and five patients received 0.01 mg/kg IV pancuronium (pancuronium group), the last three groups being injected 5 min before receiving 1 mg/kg IV succinylcholine. The doses of *d*-tubocurarine, vecuronium, and pancuronium that were selected represent those that produce neuromuscular blockade equal to that produced by 0.04 mg/kg alcuronium (2), which was used for pretreatment in our previous study (1).

Premedication consisted of 0.008 mg/kg scopolamine given intramuscularly 30 min before induction of anesthesia. Before induction, while patients were under local anesthesia with 0.5% lidocaine, 22-gauge catheters were placed in the superficial dorsal vein for infusion of drugs and lactated Ringer's solution, as well as the radial artery for collection of blood samples. Anesthesia was induced with 3 mg/kg thiopental followed by 3% enflurane in oxygen. Stimulation of the patients was avoided during the study period, and tracheal intubation was delayed until after the collection of the last blood sample. The time between the administration of thiopental and the injection of either saline or succinylcholine was 15 min in all groups.

The intensity of fasciculations was evaluated visually and was scored from 0 to 3 (0, no fasciculations; 1, fibrillations just visible; 2, moderate contractions; and 3, vigorous contractions) (3). Samples of arterial blood for measurement of plasma norepinephrine and epinephrine concentrations were drawn immediately before (baseline), and 1, 3, 5, and 10 min after, intravenous succinylcholine. At the same time intervals, systolic blood pressure was measured using the auscultatory method, and heart rate was displayed digitally on a Nihon Kohden model 11 polygraph (Tokyo, Japan). Samples for the analyses of plasma catecholamine concentrations (5 mL) were immediately placed in capped containers with EDTA·2 Na, then stored on ice and centrifuged within 15 min. The decanted plasma was stored at −40°C until analyzed for norepinephrine and epinephrine using high-performance liquid chromatography (Shimadzu LC-1, Japan) with electrochemical detection (Bioanalytical System LC3A) (4). Briefly, this method used 200 pg dihydroxybenzylamine as an internal standard, with the catecholamines being eluted with 0.1 M perchloric acid. The lower limit of detection of the assay for the catecholamines was approximately 20 pg/mL, with an overall coefficient of variation of 5%–10%. Arterial samples (3 mL) for the analyses of blood gas tensions and plasma enflurane and potassium concentrations were collected in separate syringes immediately before (baseline), and 5 and 10 min after, succinylcholine.

Statistical analyses were performed by analyses of variance (repeated measures analysis of variance) and χ^2 analyses. One-way analyses of variance with critical-difference testing were used to test the significance of differences from baseline values. χ^2 Analyses were performed to compare proportions of patients assigned to graded categories representing intensity of fasciculations. $P < 0.05$ was considered to be statistically significant.

Results

The sex distribution (male/female) and age (years) for saline, succinylcholine, *d*-tubocurarine, vecuronium, and pancuronium groups were 2/5 and 41 ± 3 (mean ± SEM), 3/4 and 43 ± 4, 3/3 and 40 ± 3, 3/4 and 39 ± 4, and 3/2 and 41 ± 4, respectively. There were no significant differences from baseline in the factors known to change plasma catecholamine concentrations, i.e., Pa_{O_2}, Pa_{CO_2}, and plasma enflurane or potassium concentrations (Table 1).

Data on plasma norepinephrine and epinephrine concentrations, systolic blood pressure, and heart rate are summarized in Table 2. In the succinylcholine group, the mean plasma norepinephrine concentrations increased and reached their maximum 3 min after the administration of succinylcholine (an increase of approximately 130%), and thereafter progressively declined until they approximated baseline levels by minute 10. A small increase in mean plasma epinephrine concentrations was also observed, but these changes did not reach statistical significance. Mean systolic blood pressure and heart rate started to increase immediately after intravenous succinylcholine, peaked at almost the same time that fasciculations became fully developed (score 2 in four patients and score 3 in three patients), and subsequently declined to the baseline levels within 10 min. In contrast, in all of the groups pretreated with either *d*-tubocurarine, vecuronium, or pancuronium, there were no significant increases in plasma catecholamine concentrations, systolic blood pressure, or

Table 1. Arterial Blood Gas Tensions and Plasma Enflurane and Potassium Concentrations

	Pao$_2$ (mm Hg)	Paco$_2$ (mm Hg)	pH	Plasma enflurane concentrations (mg/dL)	Plasma potassium concentrations (mEq/L)
Saline group ($n = 7$)					
Baseline	556 ± 12	40 ± 2	7.38 ± 0.01	15.6 ± 0.8	3.7 ± 0.1
5 min	553 ± 20	38 ± 2	7.40 ± 0.02	16.5 ± 0.6	3.7 ± 0.1
10 min	521 ± 15	39 ± 2	7.40 ± 0.02	17.5 ± 1.1	3.8 ± 0.2
Succinylcholine group ($n = 7$)					
Baseline	597 ± 14	38 ± 2	7.40 ± 0.01	15.1 ± 2.2	3.7 ± 0.2
5 min	585 ± 9	39 ± 2	7.39 ± 0.01	14.8 ± 2.3	4.1 ± 0.1
10 min	536 ± 19	40 ± 2	7.38 ± 0.01	16.4 ± 2.2	4.1 ± 0.2
d-Tubocurarine group ($n = 6$)					
Baseline	594 ± 32	41 ± 2	7.39 ± 0.02	12.8 ± 1.0	4.0 ± 0.1
5 min	586 ± 20	41 ± 2	7.39 ± 0.01	13.0 ± 0.5	4.0 ± 0.2
10 min	575 ± 17	41 ± 3	7.39 ± 0.02	14.2 ± 0.7	4.3 ± 0.2
Vecuronium group ($n = 7$)					
Baseline	594 ± 16	40 ± 1	7.38 ± 0.02	13.1 ± 1.1	3.7 ± 0.1
5 min	609 ± 14	41 ± 2	7.37 ± 0.02	12.0 ± 0.7	4.0 ± 0.2
10 min	561 ± 21	41 ± 2	7.38 ± 0.02	13.4 ± 0.7	3.9 ± 0.1
Pancuronium group ($n = 5$)					
Baseline	606 ± 21	39 ± 1	7.39 ± 0.01	14.8 ± 1.2	3.6 ± 0.2
5 min	590 ± 25	42 ± 2	7.37 ± 0.01	14.7 ± 1.0	3.8 ± 0.2
10 min	569 ± 15	41 ± 2	7.37 ± 0.02	15.1 ± 1.3	4.0 ± 0.1

All values are expressed as mean ± SEM.
There are no significant differences in this table.

heart rate, and no fasciculation occurred (score 0 in all patients) in response to succinylcholine.

Discussion

Our results show that *d*-tubocurarine, vecuronium, and pancuronium significantly and equally attenuate succinylcholine-induced increases in plasma norepinephrine concentrations, systolic blood pressure, and heart rate. *d*-Tubocurarine has a slightly greater blocking action than alcuronium on sympathetic ganglia, whereas vecuronium and pancuronium have little ganglion blocking action in the doses used clinically; autonomic margins of safety (ED$_{50}$ for autonomic inhibition/ED$_{95}$ for neuromuscular block) are 2.94, 18.0, 89.2, and 328.6 for *d*-tubocurarine, alcuronium, vecuronium, and pancuronium, respectively (2). Although these values of autonomic margin of safety are calculated based on the data obtained in the cat, there is considerable indication that if a neuromuscular relaxant produces an autonomic effect in the cat within or near its neuromuscular dose range, the neuromuscular blockade in humans will be accompanied by cardiovascular changes corresponding to those autonomic actions (2). Accordingly, if, as hypothesized in our previous study, alcuronium, which has sympathetic ganglion blocking action, combined with the nicotinic receptors at the sympathetic ganglia before the administration of succinylcholine and blocked the agonistic action of succinylcholine on these receptors (1), it is to be expected that *d*-tubocurarine will also do so, but that vecuronium and pancuronium will not attenuate succinylcholine-induced increases in plasma levels of norepinephrine. However, contrary to our expectations, all of the nondepolarizing neuromuscular relaxants given before succinylcholine in the present study attenuated these cardiovascular effects of succinylcholine to a significant extent, regardless of the presence or the absence of their sympathetic ganglion blocking action. These results suggest that the interaction between succinylcholine and *d*-tubocurarine, vecuronium, or pancuronium at the nicotinic receptors on the sympathetic ganglia has little effect, if any, on attenuation of succinylcholine-induced increases in plasma levels of norepinephrine.

Thus far, all published discussions regarding the effects of succinylcholine on nicotinic receptors have been limited to the postsynaptic receptors localized either at the skeletal neuromuscular junction or in the autonomic ganglia (see Figure 1 of Reference 5 or Figure 4-7 of Reference 6). It has, however, recently been postulated that presynaptic nicotinic receptors at or near the postganglionic sympathetic terminals might be involved in cholinergic transmission and in

Table 2. Plasma Norepinephrine and Epinephrine Concentrations, Systolic Blood Pressure, and Heart Rate

	Plasma norepinephrine concentrations (pg/mL)	Plasma epinephrine concentrations (pg/mL)	Systolic blood pressure (mm Hg)	Heart rate (beats/min)
Saline group (*n* = 7)				
Baseline	250 ± 92	101 ± 24	99 ± 6	76 ± 2
1 min	244 ± 82	97 ± 24	95 ± 4	74 ± 2
3 min	216 ± 71	94 ± 17	91 ± 3	73 ± 2
5 min	237 ± 86	115 ± 41	94 ± 4	72 ± 2
10 min	219 ± 66	111 ± 27	88 ± 3	68 ± 2
Succinylcholine group (*n* = 7)				
Baseline	187 ± 39	115 ± 16	93 ± 2	77 ± 4
1 min	308 ± 60	167 ± 39	120 ± 7[a]	102 ± 6[a]
3 min	429 ± 61[a]	153 ± 28	120 ± 7[a]	89 ± 6
5 min	293 ± 36	172 ± 42	96 ± 4	81 ± 5
10 min	219 ± 41	124 ± 29	88 ± 2	76 ± 5
d-Tubocurarine group (*n* = 6)				
Baseline	227 ± 50	121 ± 23	95 ± 4	80 ± 4
1 min	194 ± 27	151 ± 31	93 ± 3	82 ± 4
3 min	196 ± 50	142 ± 20	92 ± 2	78 ± 4
5 min	196 ± 39	123 ± 30	93 ± 4	77 ± 5
10 min	216 ± 49	152 ± 37	86 ± 3	71 ± 4
Vecuronium group (*n* = 7)				
Baseline	224 ± 47	147 ± 31	83 ± 6	74 ± 6
1 min	238 ± 55	150 ± 47	84 ± 5	74 ± 6
3 min	236 ± 48	173 ± 41	82 ± 6	73 ± 6
5 min	235 ± 46	157 ± 30	82 ± 6	73 ± 6
10 min	231 ± 50	146 ± 41	77 ± 5	69 ± 5
Pancuronium group (*n* = 5)				
Baseline	236 ± 68	150 ± 42	100 ± 5	88 ± 12
1 min	231 ± 36	134 ± 42	98 ± 4	87 ± 12
3 min	277 ± 85	152 ± 63	102 ± 3	88 ± 11
5 min	217 ± 37	154 ± 57	99 ± 5	86 ± 12
10 min	253 ± 81	166 ± 61	93 ± 6	81 ± 12

All values are expressed as mean ± SEM.

[a] $P < 0.05$ compared with baseline values.

the actions of various drugs (6). This hypothesis is supported by the fact that nicotinic agonists cause the release of catecholamines, predominantly norepinephrine, in a number of isolated tissues or organs devoid of ganglionic cells. Nicotine or acetylcholine (the latter in the presence of atropine) produces positive inotropic effects in isolated rabbit hearts perfused by means of a modified Langendorff apparatus (7), contraction of the isolated spleen of the dog (8), and constriction of the perfused isolated central ear artery of the rabbit (9). Based on these observations, Nigrovic et al. (10,11) postulated that succinylcholine-induced release of catecholamines would result from the agonistic action of succinylcholine on the nicotinic receptors at or near the postganglionic sympathetic terminals. Although the present study does not permit any definitive conclusion regarding the possible interaction between succinylcholine and *d*-tubocurarine, vecuronium, or pancuronium at the receptor level, the results obtained in the present study showing that the nicotinic receptors on the sympathetic ganglia are not the sites of interaction between succinylcholine and neuromuscular relaxants used for pretreatment suggest the possibility that the presynaptic nicotinic receptors on the postganglionic sympathetic terminals might be involved in the interaction between these drugs.

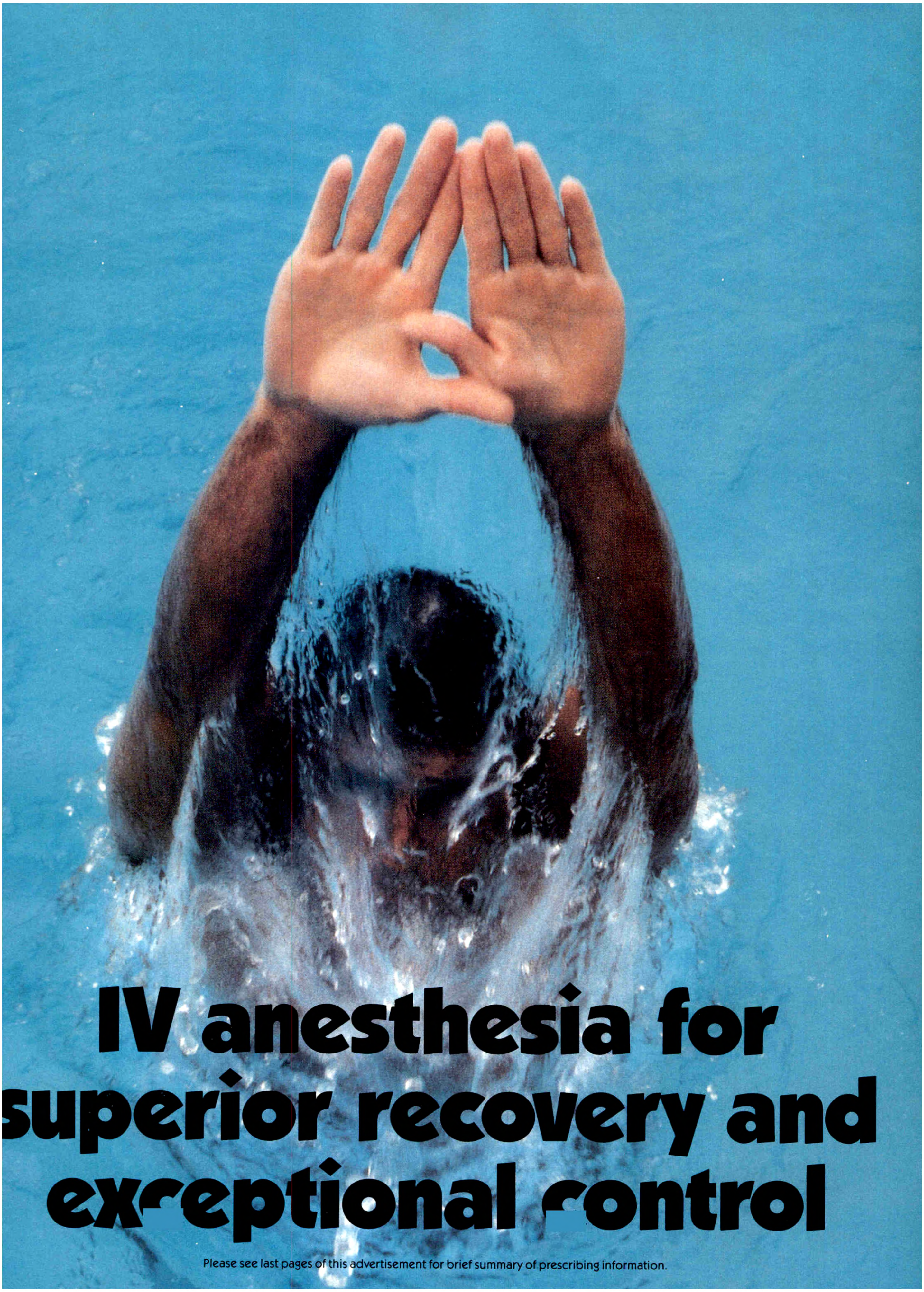
The nicotinic receptors of autonomic ganglia have certain features in common with those at the motor end plate, but the two types are not identical: they respond differently to certain stimulating and blocking agents (6). Hence, Weiner and Taylor designated the former as N_G and the latter as N_M (6). In the present study, although the magnitude of the sympathetic ganglion blocking action, i.e., the antagonistic action on N_G, is different in *d*-tubocurarine, vecuronium, and pancuronium, these neuromuscular relaxants significantly and equally attenuated fasciculations as well as succinylcholine-induced increases in plasma levels of norepinephrine. These results suggest that, if the presynaptic nicotinic receptors on the postganglionic sympathetic terminals are involved in the interaction of the neuromuscular relaxants studied here, these presynaptic nicotinic receptors would resemble in character N_M rather than N_G.

Similar to the results of our previous study (1) and to those of Nigrovic et al. (10), succinylcholine significantly increased plasma norepinephrine concentrations without significant increases in plasma epinephrine concentrations, suggesting that it stimulates the nicotinic receptors either in the autonomic ganglia or on the postganglionic sympathetic terminals, but has little effect, if any, on the nicotinic receptors of the adrenal medulla. If the nicotinic receptors of the adrenal medulla were equally stimulated by succinylcholine, plasma levels of both norepinephrine and epinephrine would increase significantly. Sumikawa et al. (12) revealed that succinylcholine has no effect on catecholamine release from isolated bovine adrenal medulla.

In summary, *d*-tubocurarine, vecuronium, and pancuronium equally attenuated the succinylcholine-induced increases in plasma norepinephrine concentrations, systolic blood pressure, and heart rate to a significant extent, regardless of the presence or the absence of their sympathetic ganglion blocking action. These results suggest that the interaction between succinylcholine and *d*-tubocurarine, vecuronium, or pancuronium at the nicotinic receptors on the sympathetic ganglia has little effect, if any, on the attenuation of succinylcholine-induced increases in plasma levels of norepinephrine. These results also suggest the possible involvement of the presynaptic nicotinic receptors at or near the postganglionic sympathetic terminals in the interaction between these drugs.

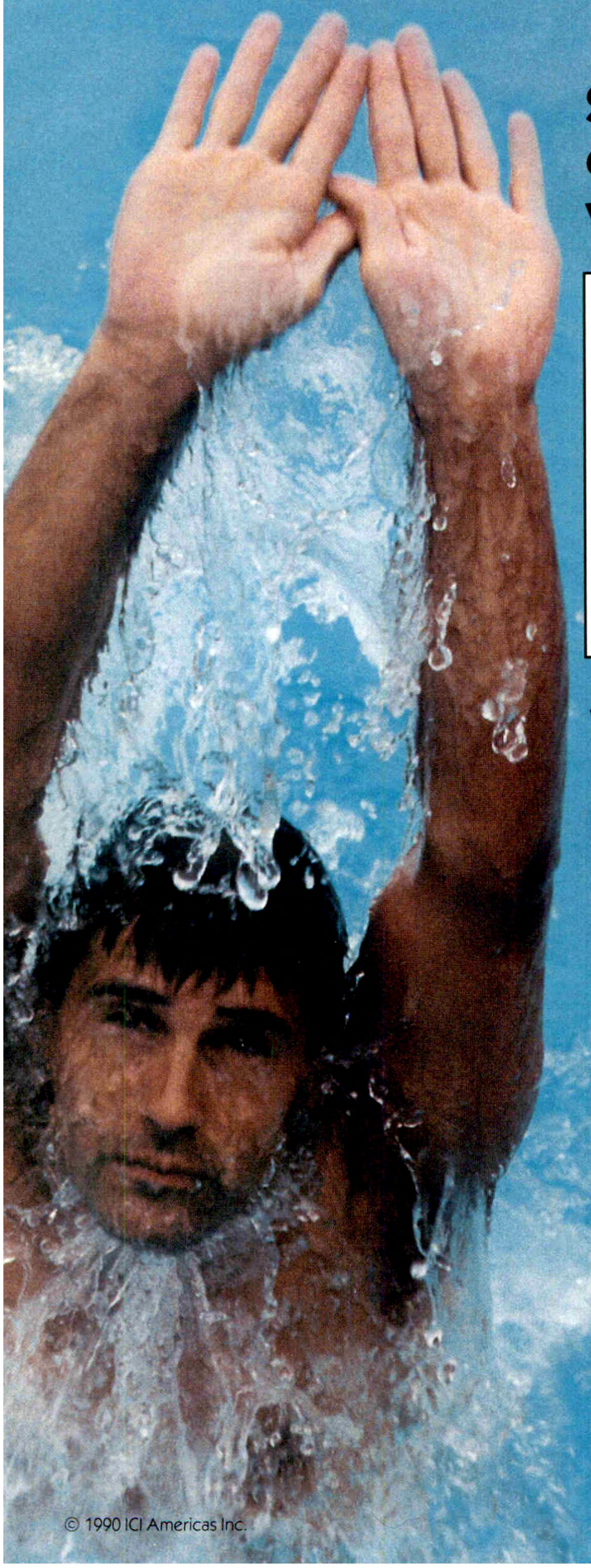
References

1. Oshita S, Tamura H, Masuda T, Fukuda S, Takeshita H. Alcuronium pretreatment attenuates succinylcholine-induced increases in plasma catecholamine concentrations in humans. Anesth Analg 1987;66:314–6.
2. Scott RPF, Savarese JJ. The cardiovascular and autonomic effects of neuromuscular blocking agents. In: Katz RL, ed. Muscle relaxants: basic and clinical aspects. Orlando, Fla.: Grune & Stratton, 1984:117–41.
3. Manchikanti L, Grow JB, Colliver JA, Canella MG, Hadley CH. Atracurium pretreatment for succinylcholine-induced fasciculations and postoperative myalgia. Anesth Analg 1985;64:1010–4.
4. Shibata O, Tsuji K, Haseba S, et al. Increased conjugated catecholamines in urine and blood after removal of pheochromocytoma. Jpn J Anesth 1985;34:434–9.
5. Bowman WC. Non-relaxant properties of neuromuscular blocking drugs. Br J Anaesth 1982;54:147–60.
6. Weiner N, Taylor P. Neurohumoral transmission: the autonomic and somatic motor nervous systems. In: Gilman AG, Goodman LS, Rall RW, Murad F, eds. The pharmacological basis of therapeutics. 7th ed. New York: Macmillan, 1985:66–99.
7. Richardson JA, Woods EF. Release of norepinephrine from the isolated heart. Proc Soc Exp Biol Med 1959;100:149–51.
8. de Burgh Daly M, Scott MJ. The effects of acetylcholine on the volume and vascular resistance of the dog's spleen. J Physiol 1961;156:246–59.
9. Steinsland OS, Furchgott RF. Vasoconstriction of the isolated rabbit ear artery caused by nicotinic agonists acting on adrenergic neurons. J Pharmacol Exp Ther 1975;193:128–37.
10. Nigrovic V, McCullough LS, Wajskol A, Levin JA, Martin JT. Succinylcholine-induced increases in plasma catecholamine levels in humans. Anesth Analg 1983;62:627–32.
11. Nigrovic V. Succinylcholine, cholinoceptors and catecholamines: proposed mechanism of early adverse haemodynamic reactions. Can Anaesth Soc J 1984;31:382–94.
12. Sumikawa K, Yoshikawa K, Amakata Y, Izumi F. The effect of muscle relaxants on catecholamine release from bovine adrenal medulla. Jpn J Anesth 1976;25:349–56.



Please see last pages of this advertisement for brief summary of prescribing information.

Superior exceptional



Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

© 1990 ICI Americas Inc.

recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®

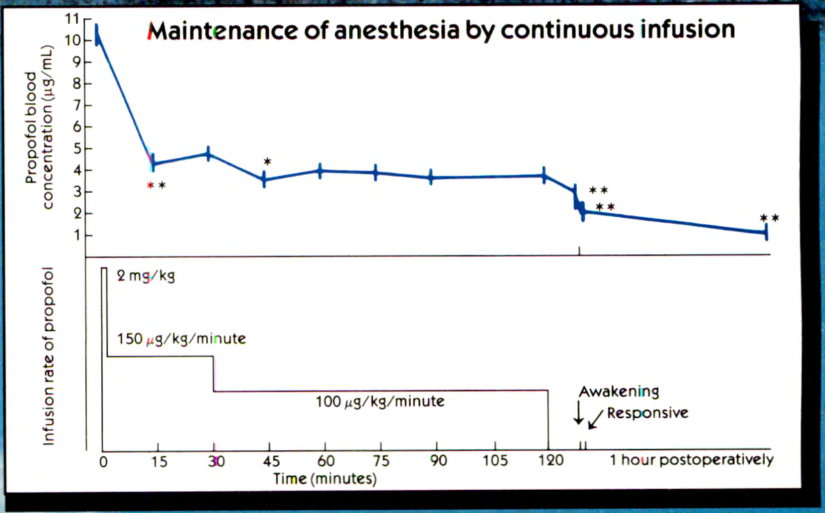
INJECTION

propofol

Superior exceptional

Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration


Maintenance of anesthesia by continuous infusion

—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

ecover[illegible], and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Since the vehicle (soybean oil in water emulsion) is capable of supporting rapid growth of microorganisms, strict aseptic technique must always be maintained while handling DIPRIVAN Injection. (See WARNINGS and DOSAGE AND ADMINISTRATION sections in the brief summary of prescribing information at the end of this advertisement.)

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.

[†] Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®
INJECTION
propofol

For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: **1.** Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. **2.** Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. **3.** Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. **4.** Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. **5.** Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

Please see last pages of this advertisement for brief summary of prescribing information.

STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

DIPRIVAN®

INJECTION
10 mg/mL
propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.)*

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should then commence without extended delay.

DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure.

Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness.

Rev. X 06/90

Made in Sweden
Manufactured for:
STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

NEW
First Issue
October
1990

An important new resource in epidemiology

ANNALS OF EPIDEMIOLOGY

Co-Editors-in-Chief: Charles H. Hennekens, MD, and Julie E. Buring, DSc, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA

Annals of Epidemiology is a new international journal publishing reports of original research in the epidemiology of chronic and acute diseases for clinicians as well as public health researchers. The journal covers research on the distribution and determinants of the current leading causes of morbidity and mortality in both developed and developing countries, including:

- coronary heart disease
- cancer
- infectious diseases
- birth defects
- injuries
- stroke
- AIDS
- alcoholism & drug addiction
- diseases of aging
- respiratory diseases

Sponsored by the *American College of Epidemiology*, **Annals of Epidemiology** is headed by an international editorial board bringing you the newest advances from around the world. **Annals of Epidemiology** features:

- *original reports* describing the results of new epidemiologic research
- *review articles* summarizing the current status of knowledge in important areas of epidemiology, either established or developing
- *specially selected proceedings* from various international symposia

In addition to these articles, **Annals of Epidemiology** is packed with pertinent information in the form of brief reports, methodologic issues involved in conducting epidemiologic research, editorials, and letters to the editor.

The primary focus of all articles is on new developments concerning issues of major importance in clinical medicine and public health.

Don't miss a single issue! Subscribe to this invaluable resource today.

Subscription Information
Volume 1, 1990-91 (6 issues in one volume)
• ISSN 1047-2729 • Institutional Rate: $125.00 • Individual Rate: $85.00*
• Subscribers outside the U.S., please add $26.00 for postage & handling.
*Individual subscriptions must be paid by personal check or charge card.

Return subscription orders to: Elsevier Science Publishing Co., Inc. • Attn: S. Roberts • P.O. Box 882, Madison Square Station • New York, NY 10159

Send sample copy requests to: *In North America* • **Elsevier Science Publishing Co., Inc.** • Attn: Journal Information Center • P.O. Box 882, Madison Square Station • New York, NY 10159

Outside North America • **Elsevier Science Publishers** • P.O. Box 211 • 1000 AE, Amsterdam • The Netherlands

For Faster Service, call or fax today to place your order:
Telephone #: (212) 633-3950 Fax #: (212) 633-3880

Note: All subscriptions begin with the first issue of the calendar year and are entered upon receipt of payment. Subscription rates valid through December 31, 1991. Please allow 6-8 weeks for delivery of the first issue.

ELSEVIER 9/90 X7A1 BISR003A

"I was immediately impressed with the breadth of topics covered... In order to evaluate the book as a reference text, I put it into service in our Drug Information Center for one month. We found answers to around 85 percent of our questions; those not found were candidates for searches of the primary literature, not a general reference work."

—DICP, The Annals of Pharmacotherapy

PHARMACOTHERAPY
A Pathophysiologic Approach

Edited by:
Joseph T. DiPiro, PharmD, University of Georgia
Robert L. Talbert, PharmD, University of Texas
Peggy E. Hayes, PharmD, Virginia Commonwealth University
Gary C. Yee, PharmD, University of Florida
L. Michael Posey, PAS Pharmacy/Association Services

By stressing the underlying pathophysiology, this outstanding reference is one of the most comprehensive texts available on pharmacotherapeutics — and an invaluable reference for the practicing physician. This superb text will be a *key* aid in choosing the best drug therapy for your patients. You'll have at your fingertips the expertise of over 150 highly regarded clinical pharmacists, helping you to understand the best strategies in rational drug therapy for *all* the major disease states.

"The listing of authors reads like a 'Who's Who' in clinical pharmacy."

—DICP, The Annals of Pharmacotherapy

This extensive volume of 1,730 pages includes in-depth sections on the pharmacological treatment of cardiovascular, respiratory, gastrointestinal, renal, neurologic, psychiatric, oncologic, and nutritional disorders. There is also an excellent section on infectious diseases, providing much needed information in this critical area. In addition, the book has specific chapters devoted to important adverse drug effects.

1989 1,730 pages cloth 0-444-01323-7 $89.50 (Dfl. 171.00 outside North America)

Send orders to:
in North America:
Elsevier Science Publishing Co., Inc.
Attn: M. Fastiggi
Box 882, Madison Square Station
New York, NY 10159

in the rest of the world:
Elsevier Science Publishers
Direct Mail Department
Box 211
1000 AE Amsterdam
The Netherlands

For faster service, phone (212) 633-3650 or FAX (212) 633-3880.

Note: Price subject to change without notice

ELSEVIER 2/90 X4A1

Shield against surgical stress

SUFENTA™

(sufentanil citrate) Injection CII

For longer more stressful procedures

As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Predictable control of stress responses from induction through recovery

***REDUCES** stress response to intubation and surgical stimulation*[1,2]

***PROVIDES** intraoperative hemodynamic stability*

***CONTROL** of the stress response is associated with less postoperative morbidity*[3,4]

***MAINTAINS** postoperative analgesia with faster recovery of respiratory drive*[5]

*References: **1.** de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology. 1982;56:112-118. **2.** Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg. 1985;64:897-910. **3.** Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology. 1986;65:A516. Abstract. **4.** Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stresss associated with worse outcome? Anesthesiology. 1987;67:A1. Abstract. **5.** Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology. 1987;66:130-135.*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

world leader in anesthesia research

JANSSEN
PHARMACEUTICA

March 1986, March 1987
U.S Patent No. 3,998,834
7618505-M

Piscataway, NJ 08854

© Janssen Pharmaceutica Inc. 1989 JPI-SU-025A-R

- Original papers
- Editorials and Editorial Notes
- Brief Reports
- Reviews

International Journal of CARDIOLOGY

Informative - Controversial - A Truly International Journal

EDITORS

ROBERT H. ANDERSON, National Heart & Lung Institute, Dovehouse Street, London SW3 6LY, UK
MICHAEL TYNAN, Guy's Hospital, St. Thomas Street, London SE1 9RT, UK
CHUICHI KAWAI, Third Division, Department of Internal Medicine, Kyoto University Hospital, 54 Kawaracho Shogoin, Sakyo-ku, Kyoto 606, Japan
ROBERT L. FRYE, Department of Internal Medicine, The Mayo Clinic, 200 1st Street S.W., Rochester, MN 55905, USA; RAYMOND GIBBONS and BERNARD GERSH, Department of Cardiovascular Diseases, The Mayo Clinic, 200 1st Street S.W., Rochester, MN 55905, USA

SCOPE

The *International Journal of Cardiology* is devoted to cardiology in the broadest sense. Both basic research and clinical papers may be submitted, but articles on the fundamental principles of cardiology will also be considered for publication. The journal serves the interest of both practicing clinicians and research workers. Editorials, Brief Reports and Review Articles covering recent developments are included. Controversial techniques, issues on Health Policy and Social Medicine are discussed and serve as useful tools for encouraging debate.
The *International Journal of Cardiology* covers the fields listed below.

EDITORIAL BOARD

Cardiovascular Research
Allen Cowley Jr., Milwaukee, U.S.A.
David A.S.G. Mary, Leeds, U.K.
Winifred Nayler, Melbourne, Australia
Gabor Rubanyi, Rochester, MN, U.S.A.
Thomas W. Smith, Boston, U.S.A.
Michihiko Tada, Osaka, Japan

Cardiac Catheterization and Invasive Techniques
David Faxon, Boston, U.S.A.
M. Kaltenbach, Frankfurt Am Main, F.R.G.
Carl Pepine, Gainesville, U.S.A.
Peter Rentrop, New York, U.S.A.
Shigetake Sasayama, Toyama, Japan

Cardiology in the Young
Valmir F. Fontes, Sao Paulo, Brazil
Robert M. Freedom, Toronto, Canada
Edward L. Kaplan, Minneapolis, U.S.A.
Douglas S. Moodie, Cleveland, U.S.A.
Norman H. Silverman, San Francisco, U.S.A.
Madison S. Spach, Durham, U.S.A.
James L. Wilkinson, Parkville, Australia

Cardiovascular Surgery
Philip B. Deverall, London, U.K.
G. Kaiser, St. Louis, U.S.A.
Guillermo Kreutzer, Buenos Aires, Argentina
Fernando A. Lucchese, Porto Alegre, Brazil
Bruce A. Reitz, Baltimore, U.S.A.

Clinical Cardiology
Fulvio Camerini, Trieste, Italy
Douglas A. Chamberlain, Brighton, U.K.
David P. de Bono, Edinburgh, U.K.
Henri Denolin, Brussels, Belgium
Gottlieb C. Friesinger, Nashville, U.S.A.
Valentin Fuster, New York, U.S.A.
Clive E. Handler, London, U.K.
K.I. Lie, Groningen, The Netherlands
Bernard Lown, Boston, U.S.A.
Lars Mogensen, Stockholm, Sweden
Matoomi Nakamura, Fukuoka, Japan
Paul J. Oldershaw, London, U.K.
Robert A. O'Rourke, San Antonio, U.S.A.
Aubrey Pitt, Prahran, Australia
Edward B. Raftery, Harrow, U.K.
Norman Sharpe, Auckland, New Zealand
Desmond Sheridan, London, U.K.
James T. Willerson, Houston, U.S.A.

Electrophysiology
Rodney S. Bexton, Newcastle, U.K.
Felix I.M. Bonke, Maastricht, The Netherlands
Nancy C. Flowers, Augusta, U.S.A.
J. Warren Harthorne, Boston, U.S.A.
Ralph Lazzara, Oklahoma City, U.S.A.
Erik Orinius, Stockholm, Sweden
Edgar Sowton, London, U.K.
Yoshio Watanabe, Toyoake, Aichi, Japan

Hypertension
William A. Littler, Birmingham, U.K.
Teruo Omae, Suita, Japan
Robert G. Wilcox, Nottingham, U.K.
Yukio Yamori, Izumo, Japan

Imaging
George A. Beller, Charlottesville, U.S.A.
Derek Gibson, London, U.K.
Gerald M. Pohost, Birmingham, U.S.A.
Nathaniel Reichek, Philadelphia, U.S.A.
Joseph R.T.C. Roelandt, Rotterdam, The Netherlands
Martin G. St. John Sutton, Boston, U.S.A.
A. Jamil Tajik, Rochester, MN, U.S.A.

Pathology
Anton E. Becker, Amsterdam, The Netherlands
Gaetano Thiene, Padua, Italy
Bruce F. Waller, Indianapolis, U.S.A.

Pharmacology
J. Thomas Bigger, Jr., New York, U.S.A.
Kanu Chatterjee, San Francisco, U.S.A.
Joseph A. Franciosa, East Rutherford, U.S.A.
Udho Thadani, Oklahoma, U.S.A.
Hisakazu Yasuda, Sapporo, Japan

Epidemiology and Biostatistics
Henry Blackburn, Minneapolis, U.S.A.
Eugene H. Blackstone, Birmingham, U.S.A.
Lila Elveback, Rochester, MN, U.S.A.
Paul Meier, Chicago, U.S.A.

CONSULTING EDITOR
Howard B. Burchell, Minneapolis, U.S.A.

Cited/abstracted in: Current Contents (Life Sciences; Clinical Medicine), Excerpta Medica (EMBASE), Index Internacional de Cardiologia; Index Medicus (MEDLINE)

SUBSCRIPTION INFORMATION
1991: Volumes 30-33 (4 volumes in 12 issues)
Institutional Rate: Dfl. 1304.00/US$ 652.00
A Personal Rate is available - apply to the Publisher for details. Prices include postage and handling.
ISSN 0167-5273

ELSEVIER

For further information and/or FREE SAMPLE COPY please write to:

In the U.S.A. and Canada:
ELSEVIER SCIENCE PUBLISHING CO., INC.,
P.O. Box 882, Madison Square Station,
New York, NY 10159, U.S.A.

In all other countries:
ELSEVIER SCIENCE PUBLISHERS
P.O. Box 211, 1000 AE Amsterdam,
The Netherlands.

Please send your orders to the Amsterdam address.
A given Dutch guilder price is definitive. Prices are excl. B.T.W. for Dutch customers.

01-103/dtpgvl/0690/074

If You're Looking For The Best Anesthesiology Billing and Practice Management System, We've Got Your Number.

1-800-2GET-NHS

Call us today, and we'll send you a free information kit on the best computer system designed exclusively for anesthesiologists —The ULTRA Anesthesiology Billing and Practice Management System from Northern Health Systems.

You'll receive all of the information you need to automate your growing practice.

Information that will improve the efficiency of your office and speed your cash flow.

You'll discover a feature-packed system that can give you instant patient information. Simplify your accounting. Process your claims electronically. Produce customized reports. And much, much more.

Call us toll-free at 1-800-2GET-NHS for your free information kit. It's the only number you need.

NHS Northern Health Systems, Inc.
5500 Corporate Drive, Pittsburgh, PA 15237

The Netherlands JOURNAL OF MEDICINE

A CURRENT AND RELIABLE SOURCE OF INFORMATION FOR THE INTERNAL MEDICINE SPECIALIST

PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

Editor-in-Chief:
P.W. DE LEEUW, *Zuiderziekenhuis, Rotterdam, The Netherlands*
Associate Editors:
A.E. MEINDERS, *Leiden, The Netherlands*
A.J.M. VOGTEN, *Heemstede, The Netherlands*

Aims and Scope:

The Netherlands Journal of Medicine publishes original articles and reviews in all relevant fields of internal medicine. In addition to clinically oriented papers, manuscripts containing experimental data, including both laboratory and animal studies, are considered for publication. The **"Brie Reports"** section allows for the publication of concise reports on original work, while **Case Reports**, which are relevant for understanding the pathophysiology or clinical presentation of internal diseases may also be accepted under this heading. Furthermore, book reviews and a correspondence section are regular items in the Journal.

An International Advisory Board has been established, consisting of outstanding scientists, all distinguished investigators in various fields of interm medicine.

Since 1987 the Journal has been published in two editions: a monthly edition for the Netherlands audience and a bimonthly edition for the international audience.

Editorial Board

T.E.W. Feltkamp, *Amsterdam*
C.L.A. van Herwaarden, *Nijmegen*
R.S.G. Holdrinet, *Nijmegen*
L. Kater, *Utrecht*
A.L.M. Kerremans, *Helmond*
E.A.R. Knot, *Rotterdam*
R. Krediet, *Amsterdam-Zo*
J.F.F. Lekkerkerker, *Enschede*
J.H.M. Lockefeer, *Oisterwijk*
A.C. Nieuwenhuijzen Kruseman, *Maastricht*
L.B.A. van de Putte, *Nijmegen*
P.J.G.M. Rietra, *Amsterdam*
W.J. Remme, *Rotterdam.*
B. Sangster, *Bilthoven*
A.J.P.M. Smout, *Utrecht*
G. Stoter, *Rotterdam*
J. Thompson, *Leiden*

International Advisory Board

A. Amery, *Leuven, Belgium*
G.M. Besser, *London, U.K.*
C.J. Bulpitt, *London, U.K.*
D.L. Clement, *Gent, Belgium*
R.D. Cohen, *London, U.K.*
A.J. Czaja, *Rochester, MN, U.S.A.*
R.H. Dowling, *London, U.K.*
S. Hadziyannis, *Athens, Greece*
N. Lameire, *Gent, Belgium*
N. McIntyre, *London, U.K.*
T. Omae, *Osaka, Japan*
M. Uribe, *Mexico D.F., Mexico*
R. Vandongen, *Perth, Australia*
P.M. Vanhoutte, *Houston, TX, U.S.A.*
M.H. Weinberger, *Indianapolis, IN, U.S.A.*

Cited/abstracted in: Current Contents (Clinical Medicine); Index Medicus (MEDLINE); Excerpta Medica (EMBASE); BIOSIS Database

Subscription information (Intl.Ed.):

1991: Vols. 38-39 (2 vols. in 12 issues)
Institutional rate: Dfl. 760.00/US$ 380.00
A Personal rate is available. Apply to the Publisher for details.
Prices include postage and handling costs.
ISSN 0300-2977

ELSEVIER SCIENCE PUBLISHERS

For further information and/or FREE SAMPLE COPY, write to:

In the USA or Canada:
ELSEVIER SCIENCE PUBLISHING CO. INC.,
P.O. Box 882, Madison Square Station,
New York, NY 10159, U.S.A Tel: (212) 633-3750

In all other countries:
ELSEVIER SCIENCE PUBLISHERS
P.O. Box 211, 1000 AE Amsterdam,
The Netherlands.

Please send your orders to the Amsterdam address
The Dutch Guilder (Dfl.) price is definitive. US$ prices are subject to exchange rate fluctuations. Prices are excl. BTW for Dutch residents.

Pediatric Anesthesiologist

Pediatric Anesthesiologist (BC/BE) is needed for a large university practice. Experience in all types of pediatric anesthesia required. Interest in research and teaching highly desirable. Present staff of 25 MDs, over 40 CRNAs and over 20 residents provides challenging anesthesia care team setting. OR area contains state-of-the-art equipment in 20 new or renovated suites.

Albany Medical Center, a 674-bed tertiary care teaching center is centrally located in beautiful upstate New York. The area offers a wealth of recreational, cultural and educational opportunities.

Interested applicants should send resume to: Dr. Philip Lumb, Professor and Chairman, Albany Medical College, Department of Anesthesiology A-131, New Scotland Avenue, Albany, NY 12208.

EEO/AA Employer M/F/H

ALBANY MEDICAL CENTER

ANESTHESIOLOGIST

West Virginia University (WVU) Health Sciences Center. Department of Anesthesiology. is recruiting for an anesthesiologist. Our Department currently has 15 faculty members and sponsors an approved residency training program, which has 24 residents.

Requirements for entry as Assistant Professor include comple-ion of CA III or fellowship year. with Board Certification preferred. An outstanding teaching opportunity is provided as esident and medical student education represent the primary mission of the Department. Consideration for either a research or a clinical track will be based on candidate background and preference. Interest in anesthesia for pediatrics. obstetrics. neurosurgery. and pain management is desirable.

WVU is in Morgantown. West Virginia. approximately 75 miles south of Pittsburgh on major interstate highways. The area. providing abundant recreation for all seasons. is situated in the scenic Allegheny Highlands region.

Clinical services are provided at the Ruby Memorial Hospital. a ertiary care center which opened in July. 1988. This $87 million. 76-bed facility features 12 operating rooms. all with state-of-he-art equipment.

As evidence of tremendous institutional growth is the new $25 million Physician Office Center. which houses the largest multispecialty group practice in the State: the new Cancer Center. which is the State's only NCI-designated cancer research cen-er: Chestnut Ridge Hospital. a 70-bed psychiatric hospital for comprehensive inpatient and outpatient care: and a 60-bed rehabilitation hospital. now under construction.

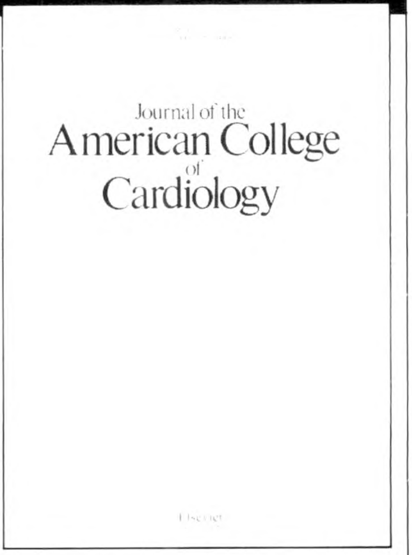
WVU is an Equal Opportunity/Affirmative Action Institution.

For additional information. contact: Edward Stullken. M.D.. Chairman. Department of Anesthesiology. WVU Health Sciences Center. Morgantown. WV 26506. Telephone: (304) 293-411.

Follow the Leader in Cardiology

Read **JACC** monthly

Journal of the
American College
of
Cardiology



Journal of the
American College
of
Cardiology

Elsevier

The **Journal of the American College of Cardiology, JACC,** is the leading journal in cardiology. **JACC's** timely coverage of clinically relevant information on the diagnosis and treatment of cardiovascular diseases has made it a favorite among cardiologists worldwide.

Why not join the thousands of your colleagues who have made reading **JACC** a part of their regular routine?

Read the **Journal of the American College of Cardiology** each month and you will find a superb collection of original articles, clinical reviews, special reports, and editorials at the forefront of cardiovascular medicine. **JACC's** comprehensive focus and distinguished editorial board assure you the most significant new information—information that you can apply directly to your practice.

Discover why **JACC** is the #1 journal in cardiology. Enter your subscription today and follow the most current and authoritative source on important developments in cardiology.

Journal of the American College of Cardiology
Volumes 17, 18 (14 issues + 1 supplement)
ISSN 0735-1097

Personal Rate: $88.00*
Institutional Rate: $132.00
Intern/Resident Rate: $55.00†

Subscribers in the U.S., Canada, or Mexico may request air delivery for an additional $115.00. Subscribers outside the U.S. must add one of the following postage options: $60.00 (surface delivery); $160.00 (surface air lift/Europe); $210.00 (surface air lift/Japan); or $305.00 (air/rest of world).

Note: All subscriptions begin with the first issue of the calendar year and are entered upon receipt of payment. Please allow 4-6 weeks for delivery of your first journal issue. Subscription rates valid until December 31, 1991.

* The personal rate is available to individuals only. A home, hospital or medical school address must be used for delivery. Orders from non-U.S. customers must be prepaid.

† Intern/Resident Rate is valid for two years only. Please send proof of status.

For sample copies send to:
in North America: Elsevier
Science Publishing Co., Inc.,
P.O. Box 882,
Madison Square Station
New York, New York 10159
in the rest of the world:
Elsevier Science Publishers,
Direct Mail Department
P.O. Box 211, 1000 AE
Amsterdam,The Netherlands

ELSEVIER
SCIENCE PUBLISHING
COMPANY, INC

Send subscription orders to your usual supplier or the New York address. For even faster service, call (212) 633-3950 or fax (212) 633-3880

X7AQ
9/90

BIAE048A

THE PERMANENTE MEDICAL GROUP
NORTHERN CALIFORNIA

QUALITY

STABILITY

LEADERSHIP

GROWTH

SUPPORT

REWARDS

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region for additional BC/BE Anesthesiologists.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. Please call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. AA-7060, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800)777-4912. EOE

KAISER PERMANENTE
Good People. Good Medicine.

Searching for an academic position? Here's an easy way.

Academic Physician Services has established a national clearinghouse for academic physicians. In addition to our bimonthly publication, we offer continuous updates of academic positions in your specialty.

A comprehensive resource.

Medical schools and teaching hospitals throughout the U.S. list their positions in *Academic Physician.* This bimonthly directory is sent free of charge to all academic physicians, post-doctorate fellows, and senior residents, and is filled ONLY with academic positions listed by subspecialty and rank.

Equal Opportunity.

We encourage qualified women and minority physicians to use our service. All medical schools and hospitals listing with *Academic Physician* are equal opportunity employers.

Continuous updates.

New positions arrive every day. To receive the most up-to-date listings in your specialty and to assure your position on our subscription list, call today: (916) 939-4242. It's the easy way.

907 Embarcadero, Suite 1
El Dorado Hills, CA 95630
FAX (916) 939-4249
PHONE (916) 939-4242

ACADEMIC
PHYSICIAN
SERVICES

PEDIATRIC CARDIAC ANESTHESIOLOGIST

West Virginia University (WVU) Health Sciences Center, Department of Anesthesiology, is recruiting for a pediatric cardiac anesthesiologist. Our Department currently has 15 faculty members and sponsors an approved residency training program, which has 24 residents.

Requirements for entry as Assistant Professor include completion of CA III or fellowship year, with Board Certification preferred. An outstanding teaching opportunity is provided as resident and medical student education represent the primary mission of the Department. Related responsibilities include clinical anesthesia with a rare opportunity to provide anesthesia for complex congenital heart surgery in neonates, like hypoplastic left heart syndrome and arterial switch procedures. The Pediatric Cardiac Surgery Service performs 180-200 cases per year. Seven pediatric cardiologists cover the entire state through outreach clinics. Opportunities are available for collaborative research projects with the Section of Pediatric Cardiology and the Pediatric Cardiac Surgery Service.

This position requires selection of the tenure track, with its concerted research commitment. Time and start-up monies will both be available to support this research.

WVU is in Morgantown, West Virginia, approximately 75 miles south of Pittsburgh on major interstate highways. The area, providing abundant recreation for all seasons, is situated in the scenic Allegheny Highlands region.

Clinical services are provided at the Ruby Memorial Hospital, a tertiary care center which opened in July, 1988. This $87 million, 376-bed facility features 12 operating roms, all with state-of-the-art equipment.

As evidence of tremendous institutional growth is the new $25 million Physician Office Center, which houses the largest multi-specialty group practice in the State; the new Cancer Center, which is the State's only NCI-designated cancer research center; Chestnut Ridge Hospital, a 70-bed psychiatric hospital for comprehensive inpatient and outpatient care; and a 60-bed rehabilitation hospital, now under construction.

WVU is an Equal Opportunity/Affirmative Action Institution.

For additional information contact: Edward Stullken, M.D., Chairman, Department of Anesthesiology, WVU Health Sciences Center, Morgantown, WV 26506. Telephone: (304) 293-5411.

PAIN EVALUATION AND TREATMENT INSTITUTE, UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE—The Pain Evaluation and Treatment Institute is a comprehensive, university-based interdisciplinary facility dedicated to the highest standards of clinical services, education and research. The interdisciplinary staff consists of physicians, psychologists, physical therapists, occupational therapists and nurses.

The Pain Institute is seeking a flexible and innovative Pain Specialist to serve as a full-time member of a physician group currently consisting of anesthesiologists and a physiatrist. This unique position involves program development, supervision of fellows and residents, clinical research, as well as, direct clinical work with diverse pain populations.

Current clinical programs at the Pain Institute include an Acute Pain Service, Head and Facial Pain Clinic, Pain Rehabilitation Program, Cancer Pain Service, Regional Anesthesia Clinic, Back Injury Clinic, and a Work Performance Assessment and Rehabilitation Program. Research associated with each of these programs and services is currently underway.

Prior experience and academic achievement in pain medicine is desirable. The successful candidate must have the desire and ability to work with an interdisciplinary clinical and research team. M.D. degree and licensure or license eligibility in Pennsylvania required. Academic rank and salary will be commensurate with qualification.

Send C.V. and 3 reference letters to: Michael C. Brody, M.D., Medical Director, Pain Evaluation and Treatment Institute, University of Pittsburgh School of Medicine, Baum Boulevard and Craig Street, Pittsburgh, PA 15213.

Effect of Obesity on Safe Duration of Apnea in Anesthetized Humans

Holly G. Jense, MD, Stevin A. Dubin, MD, Paul I. Silverstein, DO, and
Una O'Leary-Escolas, CRNA

JENSE HG, DUBIN SA, SILVERSTEIN PI, O'LEARY-ESCOLAS U. Effect of obesity on safe duration of apnea in anesthetized humans. Anesth Analg 1991;72:89–93.

Obese patients have a decreased functional residual capacity and, hence, a reduced oxygen supply during periods of apnea. To determine whether obese patients are at greater risk of developing hypoxemia during induction of anesthesia than patients of normal weight, 24 patients undergoing elective surgical procedures were studied. Group 1 (normal) were within 20% of their ideal body weight. Group 2 (obese) were more than 20% but less than 45.5 kg over ideal body weight. Group 3 (morbidly obese) were more than 45.5 kg over ideal body weight. Patients were preoxygenated for 5 min or until expired nitrogen was <5%. After induction of anesthesia and muscle relaxation the patients were allowed to remain apneic until arterial saturation as measured by pulse oximetry reached 90%. The time taken for oxygen saturation to decrease to 90% was 364 ± 24 s in group 1, 247 ± 21 s in group 2, and 163 ± 15 s in group 3; these times are significantly different at $P < 0.05$ between groups. Regression analysis of the data demonstrated a significant negative linear correlation ($r = -0.83$) between time to desaturation and increasing obesity. These results show that obese patients are at an increased risk of developing hypoxemia when apneic.

Key Words: COMPLICATIONS, OBESITY—desaturation during apnea. VENTILATION, APNEA—desaturation in obesity.

The induction of anesthesia is associated with a variable period of apnea, which lasts until mechanical ventilation of the lungs begins or until the patient resumes spontaneous ventilation. During this time the body's continuing requirements for oxygen are supplied from the functional residual capacity (FRC). During routine anesthetic inductions, control of the airway is rapidly obtained with mask ventilation, thus minimizing the time during which the patient is dependent upon oxygen supplies in the FRC. During a rapid sequence induction, the apneic period must be maintained until the airway is protected by an endotracheal tube. If intubation proves difficult, prolongation of the apneic period may place the patient at risk of hypoxemia. Patients undergoing routine induction of anesthesia who are found to be difficult to ventilate may also be at risk of developing hypoxemia. Various preoxygenation techniques (1,2) have been advocated in attempts to denitrogenate the FRC and thereby delay the onset of hypoxia (oxygen saturation <90%). However, the actual duration of apnea before development of desaturation has been measured only in healthy patients; in these patients safe apneic periods can be as long as 8.9 min (1).

A morbidly obese patient has multiple pulmonary abnormalities, which include decreased vital capacity, expiratory reserve volume, inspiratory capacity, and FRC (3,4). Furthermore, assumption of the recumbent position for induction of anesthesia in such patients further decreases expiratory reserve volume and FRC and increases the possibility of tidal volume falling within closing capacity (4–6). The diminished FRC results in decreased stores of oxygen to meet the metabolic requirements when the patient is apneic.

The purpose of this study was to determine if there was a correlation between body mass and safe duration of apnea in the supine patient. The safe duration of apnea was defined as that period of time during which the arterial saturation as measured by pulse oximetry remained at or above 90%.

Methods and Materials

Thirty-two ASA physical status I or II patients scheduled for elective surgical procedures under general

---

Received from the Department of Anesthesiology, Medical College of Georgia, Augusta, Georgia. Accepted for publication August 14, 1990.

Address correspondence to Dr. Jense, Department of Anesthesiology, Medical College of Georgia, Augusta, GA 30912-2700.

©1991 by the International Anesthesia Research Society

anesthesia were recruited. The investigation was approved by the Medical College of Georgia Human Assurance Committee, and written informed consent was obtained from each patient. Patients with cardiovascular, pulmonary, neurologic, hematologic, or vascular disease were excluded. Patients were divided into three groups based upon ideal body weight (IBW), which was calculated by a standard formula according to the patient's height (7). Group 1 (normal) consisted of patients who were within 20% of their IBW. Group 2 (obese) contained patients who were more than 20% over IBW but less than 45.5 kg over IBW, and group 3 (morbidly obese) patients were 45.5 kg greater than IBW. Body mass index was calculated for each group by dividing weight in kilograms by the square of the height in meters. All patients were premedicated with 150 mg of oral ranitidine the night before and on the morning of surgery. No other premedication was given. On arrival in the operating room standard monitors were applied including a fingertip oximeter probe, and the pulse oximeter (Nellcor N-100) was adjusted to its rapid update mode (3 s averaging). Blood pressure, including mean arterial pressure (MAP), was measured (Critikon Dinamap Vital Signs Monitor 1846) using a blood pressure cuff of the appropriate size for each patient. If difficulty with arterial puncture was anticipated, a 22-gauge arterial catheter was inserted under local anesthesia. The arterial catheter was inserted into the arm opposite the pulse oximeter probe. The patients were instructed to breathe 100% O_2 through a clear face mask attached to a circle system with an inline mass spectrometer (Perkin-Elmer) adjusted to continuous update mode (sampling approximately every 10–15 s). A tight mask fit was maintained to ensure no entrainment of room air; this was verified by a inspired nitrogen content of less than 1% ($F_{IN_2} < 1\%$) on the mass spectrometer. Patients were preoxygenated with a 10-L/min flow until the expired nitrogen was less than 5% ($F_{EN_2} < 5\%$) or until 5 min had elapsed. Absence of rebreathing during denitrogenation was verified by $F_{IN_2} < 1\%$. Anesthesia was induced with 4–5 mg/kg thiopental, and onset of apnea determined by visual inspection of inspiratory effort and lack of carbon dioxide trace on the mass spectrometer. The patients were then manually ventilated once to ensure the ability to manage the airway. Patients were withdrawn from the study if there was any concern about the ease of manual ventilation. Succinylcholine (1 mg/kg) was given to the remaining subjects, the face mask was removed, and the subject's head was allowed to remain in an undisturbed neutral position. This time represented the start of the apneic period. A succinylcholine infusion was started and additional 100-mg doses of thiopental were given as needed to maintain blood pressure and pulse within 20% of the baseline values. A 22-gauge radial artery catheter was inserted immediately after induction, and arterial blood samples were obtained when arterial saturation on the pulse oximeter was 100% and 90%. Arterial oxygen saturation as measured by the pulse oximeter (Sp_{O_2}) was recorded until the Sp_{O_2} decreased to 90%. At this time, the duration of apnea was recorded and the patients were ventilated by mask with oxygen. An Sp_{O_2} of 90% was chosen because saturations below 90% are on the steep portion of the oxyhemoglobin dissociation curve, and, therefore, the patient would continue to have a rapid fall in saturation after this point.

Data were analyzed using analysis of variance, Student's *t*-test, and regression analysis. $P < 0.05$ was considered to be significant.

Results

A total of 24 patients were included in the results: seven in group 1, 11 in group 2, and six in group 3. Eight patients were eliminated from the study: five of the eight (one in group 1, three in group 2, one in group 3) due to concerns about the airway after one manual breath, one of the eight because of a malfunctioning pulse oximeter, another one because of development of premature ventricular beats during apnea, and one patient who did not become apneic after the initial dose of thiopental. All eight of these patients did well during the remainder of their anesthetic. Arterial blood samples were not obtained in three patients (two in group 1 and one in group 3). Four patients smoked cigarettes (one in group 1, two in group 2, and one in group 3). The smokers did not affect results when included in the statistical analysis, and so they were included in the study.

There was a trend relating age to obesity with group 1 (normal) being significantly younger (28 ± 4 yr) than group 2 (obese) (38 ± 3 yr) or group 3 (morbidly obese) (44 ± 6 yr). However, there was no significant correlation between age and safe duration of apnea as demonstrated by regression analysis of time to Sp_{O_2} of 90% compared to age, which yielded a correlation coefficient of −0.14. There were no significant differences between groups with respect to preoperative hemoglobin, baseline room air saturations, MAP at 100% saturation, MAP at 90% saturation, heart rate at 100% saturation, and heart rate at 90% saturation. A trend of increasing MAP with obesity was noticeable but did not achieve statistical

Table 1. Summary Characteristics of Each Group

	Group 1	Group 2	Group 3
n	7	11	6
BMI (kg/m^2)	22.3 ± 1.1^a	32.1 ± 0.8^a	43.2 ± 1.6^a
Percent of ideal body weight	100 ± 5^a	150 ± 5^a	213 ± 18^a
Age (yr)	28 ± 4	38 ± 3	44 ± 6
Hgb (g/dL)	12.6 ± 1.3	12.8 ± 0.6	12.6 ± 0.5
HR at Spo_2 100%	77 ± 8	93 ± 4	88 ± 9
HR at Spo_2 90%	96 ± 10	97 ± 4	98 ± 7
MAP at Spo_2 100% (mm Hg)	88 ± 4	97 ± 3	99 ± 3
MAP at Spo_2 90% (mm Hg)	95 ± 3	98 ± 4	106 ± 4

BMI, body mass index; Hgb, hemoglobin; HR, heart rate; MAP, mean arterial pressure.

All values are mean ± SE.

^{a}Significant difference between groups at $P < 0.05$.

Table 2. Summary of Respiratory Variables and Comparison of Pulse Oximetry and Sao_2 in Each Group

	Group 1	Group 2	Group 3
Sao_2 at Spo_2 of 100% (%)	97 ± 0.5	97 ± 0.5	97 ± 0.6
Sao_2 at Spo_2 of 90% (%)	88 ± 1.6	85 ± 1.4	86 ± 0.6
Pao_2 at Spo_2 of 100% (mm Hg)	433 ± 13	370 ± 24	420 ± 35
Pao_2 at Spo_2 of 90% (mm Hg)	66 ± 5.5	61 ± 3.6	59 ± 0.3
$Paco_2$ at Spo_2 of 100% (mm Hg)	39 ± 3.6	38 ± 2.1	40 ± 4
$Paco_2$ at Spo_2 of 90% (mm Hg)	56 ± 3.7	51 ± 1.9	50 ± 2.9

Sao_2, arterial oxygen saturation; Spo_2, arterial oxygen saturation as measured by the pulse oximeter; Pao_2, partial pressure of oxygen, arterial; and $Paco_2$, partial pressure of carbon dioxide, arterial.

All values are mean ± SE.

Table 3. Summary of Times to Arterial Desaturation and Denitrogenation

	Group 1	Group 2	Group 3
Time to Spo_2 90% (s)	364 ± 24^a	247 ± 21^a	163 ± 15^a
Range	274–485	90–323	120–222
FEN_2 at Spo_2 100% (%)	7.5 ± 2.4	7.2 ± 2.0	4.2 ± 0.3
Range	2.2–18.7	2.4–25	3.6–5
Time to denitrogenate (s)	235 ± 28.4	220 ± 17.5	172 ± 35
Range	120–300	155–300	82–300

Spo_2, arterial oxygen saturation as measured by the pulse oximeter; FEN_2, fractional concentration of nitrogen in expired gas.

All values are mean ± SE.

^{a}Significant difference between groups at $P < 0.05$.

significance. Body mass index was calculated for each group. The results are presented in Table 1.

All patients had an Spo_2 of 100% before induction of anesthesia. Table 2 presents blood gas tension data and oxygen saturations together with $Paco_2$ data at both 100% and 90% saturation. The samples during 100% saturation were drawn either immediately before anesthetic induction or upon insertion of the arterial catheter and therefore no comment can be made on rate of increase in CO_2 during the apneic period.

Table 3 depicts the average time to desaturation to 90%; this time was significantly different between groups. Analysis of the data demonstrates a significant negative linear correlation between time to desaturation and increasing obesity with a correlation coefficient of −0.83 (see Figure 1).

After denitrogenation of the lungs there was a trend toward a lower FEN_2 in obese patients. Obese patients also required a shorter time to achieve denitrogenation, although these two observations were not statistically significant via regression analysis.

Discussion

This study demonstrates that anesthetized, paralyzed, supine patients of normal weight are able to tolerate significantly longer periods of apnea safely than can obese and morbidly obese patients. The major factor accounting for the decreased tolerance of obese patients for periods of apnea is their marked alteration in pulmonary function related to their increased body weight. A significant abnormality in obese patients is a decrease in FRC, an average of 1.9 L in obese adult males compared to 2.6 L in lean subjects in the supine position (4). When confronted with a patient requiring emergency surgery under general anesthesia a choice must be made between a rapid sequence induction with cricoid pressure (8) or an awake intubation. If intubation proves to be difficult during a rapid sequence induction then mask ventilation of a patient with a full stomach may be necessary if the patient does not resume spontaneous ventilation before desaturation. This places the patient at increased risk for aspiration. A healthy nonobese patient can usually tolerate the period of apnea (1) required for spontaneous ventilation to resume before desaturation occurs, but, as demonstrated by this study, obese patients may not be able to tolerate this period of apnea. Additionally, morbidly obese patients may desaturate before even an uncomplicated intubation can be accomplished, as demonstrated by one patient who desaturated in less than 100 s.

The results presented in this study demonstrate a significant negative correlation between safe duration of apnea and the patient's level of obesity. Patients in

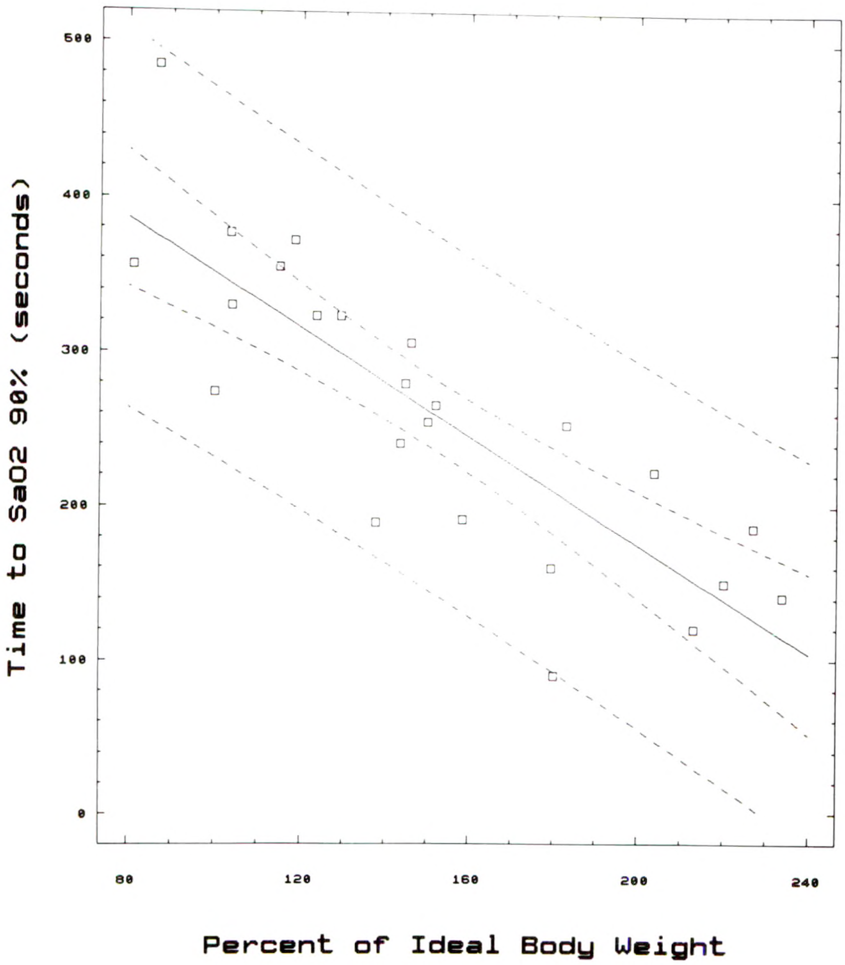


Figure 1. Regression analysis of time to reach an Spo_2 of 90% versus percent of IBW. The *inner dashed lines* are the 95% confidence interval and the *outer dashed lines* are the 95% prediction interval with a correlation coefficient of −0.83.

the morbidly obese group were unable to tolerate even 3 min of apnea with some patients beginning to desaturate within 95 s. The rapid rate of desaturation is similar to that reported in pregnant patients (9). This inability to tolerate apnea is of particular concern when a rapid sequence induction and intubation is attempted and intubation is unsuccessful. The fact that the morbidly obese patients were older (44 ± 5 yr) did not significantly affect these results, even though older patients are also known to have impaired gas exchange (10).

The finding of 6.0 ± 0.3 min to desaturation in normal weight patients differs slightly from previous authors due to a difference in timing the apneic period. Studies (1) of the duration of safe apnea in normal weight patients after different denitrogenation techniques have shown that with the 3-min technique desaturation occurred in 8.9 ± 1 min and with the four-breath technique in 6.8 ± 1.8 min. This study began timing from the moment of induction. In the present study the time from induction to onset of apnea was 45 ± 4 s. A similar study (11) of slightly older patients who smoked showed a period of only 6.8 ± 0.6 min when preoxygenating for 3 min. Prolongation of the time to desaturation in all patient groups can possibly be accomplished by apneic oxygenation via nasal insufflation of oxygen (11) or by maintaining a tight mask fit during apnea (12).

The initial studies (2) of preoxygenation before induction of anesthesia demonstrated that 3 min of breathing 100% oxygen at a 4-L/min flow via a semi-closed circle system was adequate to denitrogenate the lungs. Another report (13) recommended 5 min of preoxygenation as a safe period. A more recent study (14) reported that preoxygenation with four vital capacity breaths of oxygen is as effective as 5 min of tidal volume breathing of oxygen in increasing Pao_2. A separate group (15) evaluated these two techniques in obese patients and reported that both methods are equally efficacious in raising Pao_2 to above 300 mm Hg. During this study FEN_2 was used to measure the amount of residual air in the FRC and thus document denitrogenation. The preoxygenation time was limited to 5 min because this is the longest recommended time and probably represents the longest clinically used period of preoxygenation. Using this approach we were able to obtain a $Pa_{O_2} > 300$ mm Hg in all groups. Future studies may be useful to compare complete denitrogenation ($F_{EN_2} < 5\%$) to 5 min of preoxygenation to determine which is a better end point.

Variables other than pulmonary functions that may affect safe duration of apnea include hemoglobin levels and basal metabolic rate. Hemoglobin levels were the only variable measured in this study. Blood pressure and heart rate, however, were maintained within 20% of baseline throughout the apneic period, thereby limiting the possible increases in oxygen consumption associated with a stress response.

In conclusion, the results confirmed the clinical impression that obese patients desaturate significantly faster than normal patients with a significant negative linear correlation between time to desaturation and obesity. In morbidly obese patients the time to desaturation is only long enough to allow a single attempt at intubation in an emergency situation. These patients will uniformly require mask ventilation if intubation is unsuccessful. An awake intubation should be considered in any morbidly obese patient presenting for emergency surgery.

References

1. Gambee AM, Hertzka RE, Fisher DM. Preoxygenation techniques: comparison of three minutes and four breaths. Anesth Analg 1987;66:468–70.
2. Hamilton WK, Eastwood DW. A study of denitrogenation with some inhalation anesthetic systems. Anesthesiology 1955;16:861–7.
3. Said SI. Abnormalities of pulmonary gas exchange in obesity. Ann Intern Med 1960;53:1121–9.
4. Tucker DH, Seiker HO. The effect of change in body position on lung volumes and intrapulmonary gas mixing in patients with obesity, heart failure and emphysema. Am Rev Resp Dis 1960;82:787–91.
5. Paul RP, Hoyt JL, Boutros AR. Cardiovascular and respiratory changes in response to change of posture in the very obese. Anesthesiology 1976;45:73–8.
6. Don HF, Craig DB, Wahba WM, Couture JG. The measurement of gas trapped in the lungs at functional residual capacity and the effects of posture. Anesthesiology 1971;35:582–90.
7. Davidson MB. Diabetes mellitus and hypoglycemia. In: Hershman JM, ed. Endocrine pathophysiology. Philadelphia: Lea & Febiger, 1977:231–2.
8. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anesthesia. Lancet 1961;ii:404.
9. Archer GW, Marx GF. Arterial oxygen tension during apnoea in parturient women. Br J Anaesth 1974;46:358–60.
10. Leblanc P, Ruff F, Milic-Emili J. Effects of age and body position on airway closure in man. J Appl Physiol 1970;28:448–51.
11. Teller LE, Alexander CM, Frumin MJ, Gross JB. Pharyngeal insufflation of oxygen prevents arterial destruction during apnea. Anesthesiology 1988;69:980–2.
12. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. Anesthesiology 1959;20:789–98.
13. Dillon JB, Darsie ML. Oxygen for acute respiratory depression due to administration of thiopental sodium. JAMA 1955;159:1114–6.
14. Gold MI, Duarte I, Muracchick. Arterial oxygenation in conscious patients after 5 minutes and after 30 seconds of oxygen breathing. Anesth Analg 1981;60:313–5.
15. Moyer GA, Rein P. Preoxygenation in the morbidly obese patient (abstract). Anesth Analg 1986;65:S106.

94 ANESTH ANALG
1991;72:94–100

Clinical Evaluation of Autotransfusion During Liver Transplantation

Yoogoo Kang, MD, Shushma Aggarwal, MD, Mohamed Virji, MD, PhD,
A. William Pasculle, ScD, Jessica H. Lewis, MD, Judith A. Freeman, MD, and
Lisa K. Martin, MT (ASCP)

KANG Y, AGGARWAL S, VIRJI M, PASCULLE AW, LEWIS JH, FREEMAN JA, MARTIN LK. Clinical evaluation of autotransfusion during liver transplantation. Anesth Analg 1991;72:94–100.

The clinical suitability of intraoperative autotransfusion was evaluated in 25 patients undergoing orthotopic liver transplantation using a Cell Saver #4 (Haemonetics) with acid-citrate-dextrose anticoagulation. In the first 14 patients (phase 1), biochemical, hematologic, coagulation, and semiquantitative bacteriologic studies were performed from the collected blood, processed blood, and patients' blood before and after 500 mL of autotransfusion. The acid-citrate-dextrose solution produced adequate anticoagulation, and the system effectively removed most of the potassium, red blood cell fragments, plasma free hemoglobin, bilirubin, coagulation factors, platelets, and fibrin degradation products. Autotransfusion (500 mL) did not alter coagulation, electrolyte balance, and hematologic findings in recipients except for a clinically insignificant increase in plasma free hemoglobin. Seventeen of 56 samples of the collected blood or processed blood were positive for coagulase (-) Staphylococcus *(occasional or rare), but blood cultures before and after autotransfusion were negative in all patients. In the next 11 patients (phase 2), a quantitative bacteriologic study was performed from the collected blood, processed blood, skin, bile duct stump, peritoneal cavity, and room air using a mock reservoir. The processed blood was not transfused. All blood cultures from the patients were sterile. However, coagulase (-)* Staphylococcus *or* Bacillus *sp was seen in two cultures from skin, three from the processed blood, and three from air, suggesting that room air and skin were the sources of contamination. When the patients of the two phases of study were compared, postoperative blood cultures were all sterile, and renal function was similar. Therefore, autotransfusion appears to be clinically acceptable during liver transplantation. Occasional contamination by few bacteria appears to be insignificant in patients who receive prophylactic antibiotic therapy.*

Key Words: TRANSFUSIONS, AUTOTRANSFUSION. SURGERY, TRANSPLANTATION—liver.

Massive blood transfusion is unavoidable during orthotopic liver transplantation (OLT) because of severe perioperative coagulopathy and surgical bleeding (1). Recent improvements in monitoring and treatment of coagulation using replacement and pharmacologic therapy (2,3) and refined surgical technique incorporating venovenous bypass have decreased blood loss (4), but the average blood requirement is still more than 15 U each of red blood cells (RBC) and fresh frozen plasma (5). Oxygen-carrying capacity and hemostasis are maintained by transfusion of banked blood products during operation, but with potential complications. Inadvertent hypovolemia, anemia, and coagulopathy may result when large quantities of specific blood products are not readily available. Other complications include transmission of blood-borne infections, isoimmunization, febrile reaction, hemolytic reaction, errors in cross-matching, acidosis, electrolyte imbalance, poor RBC survival, and low level of 2,3-diphosphoglyceric acid (6–8). Transmission of viral disease and isoimmunization are particularly relevant to organ transplantation recipients. Patients who develop viral infection have a poor postoperative prognosis (9), and highly sensitized patients require more blood products and develop thrombocytopenia after OLT (10). Intraoperative autotransfusion (IAT) can minimize the complications of homologous transfusion, as has been experienced

---

Received from the Departments of Anesthesiology, Pathology, and Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Accepted for publication August 17, 1990.

Address correspondence to Dr. Kang, Department of Anesthesiology, Presbyterian-University Hospital, Desoto and O'Hara Streets, Pittsburgh, PA 15213.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

in patients undergoing cardiovascular, orthopedic, abdominal, and trauma surgery (11–14). Intraoperative autotransfusion has inherent potential complications, however (15). Hemolysis during the collection phase may lead to hemoglobinuria and renal dysfunction, and residual anticoagulants or contamination of tissue thromboplastin may cause coagulopathy. Dissemination of infection, distant metastasis of malignant cells, and air and fat emboli may also occur. Intraoperative autotransfusion has been used during OLT without complication (16–18), but it may not be clinically suitable for patients who are prone to developing coagulopathy, renal dysfunction, and infection.

This study was performed in two stages to investigate the clinical applicability and the potential complications of IAT during OLT. The first phase was a descriptive investigation of the biochemical, hematologic, semiquantitative microbiologic, and coagulation characteristics of the processed blood and its acute effects on the recipient. The results of phase 1 led to the second phase, a quantitative bacteriologic study.

Methods

Phases 1 and 2 of this study were approved by the Institutional Research Review Board, and informed consent was obtained from all patients.

Phase 1

Fourteen consecutive adult patients undergoing OLT were studied. Patients with malignancy, seropositivity for hepatitis antigen, or potential intraabdominal infection (e.g., recent history of abdominal surgery, including OLT, or spontaneous bacterial peritonitis) were excluded. Intraoperatively, lost blood volume was replaced with a fluid mixture in a ratio of RBC:fresh frozen plasma:Plasma-Lyte A (Travenol, Deerfield, Ill.) of 300:200:250 mL. All patients received prophylactic antibiotics perioperatively (1 g ampicillin and 1 g cefotaxime sodium, every 6 h).

The autotransfusion system (Cell Saver #4, Haemonetics Inc., Braintree, Mass.) has three phases: collection and anticoagulation, washing and concentration, and transfusion. Collection of the blood from the abdominal cavity began after drainage of ascites and ended before reconstruction of the biliary tract or surgical entrance to the gastrointestinal tract, to avoid contamination from ascites or enteric bacteria. One disposable double-lumen suction catheter, with a vacuum pressure of 80 mm Hg, was used to collect the blood into a cardiotomy reservoir. The reservoir was primed with 200 mL of acid-citrate-dextrose solution (ACD formula A, Travenol, Deerfield, Ill.). The blood was anticoagulated during the collection phase by a continuous infusion of acid-citrate-dextrose solution (6–8 mL/min) via a side port of the double-lumen suction catheter. The collected blood was then transferred to a centrifuge bowl, and noncellular elements were separated by a centrifugal force of 5780 rpm and discarded. Remaining RBC were washed with 1000 mL of PlasmaLyte-A solution. The washed and concentrated blood was transferred to a sterile blood transfusion bag and transfused to the patient via a 40-μm filter.

During surgery, blood samples (15 mL each) were obtained from the cardiotomy reservoir (collected blood), from the blood transfusion bag (processed blood), and from the patient via an indwelling radial arterial catheter 5 min before and 5 min after transfusion of 500 mL of the processed blood. Hematocrit and serum levels of sodium, potassium, ionized calcium, bilirubin, free hemoglobin, and citrate were measured. Blood smears were made to determine RBC morphology. Blood coagulation was assessed by measurements of coagulation factors I, II, and VIII, euglobulin lysis time, fibrin monomers (ethanol-gel test), fibrin degradation products (FDP, Wellco test), platelet count, and thrombelastography.

For the bacteriologic study, 10 mL of blood was divided into two aliquots of 5 mL each, which were inoculated into aerobic and anaerobic radiometric blood culture bottles (BBL Microbiology Systems, Cockeysville, Md.). The bottles were monitored daily for signs of growth using a Bactec blood culture instrument (Becton Dickinson Diagnostic Instrument Systems, Towson, Md.). Bacterial isolates were identified using standard methods.

Phase 2

Another 15 consecutive patients were included in this phase of the study. All preparations were the same as in phase 1, but the processed blood was not transfused to the patient. Blood samples (7.5 mL each) were obtained from the cardiotomy reservoir (collected blood), from the transfusion bag (processed blood), and from the patient during the anhepatic stage of OLT. The blood samples (5 mL each) were inoculated into a lysis-centrifugation blood culture tube (Isolator, DuPont, Wilmington, Del.). After centrifugation of the lysed blood, 0.1-mL portions were inoculated onto chocolate agar plates (BBL, Cockeys-

Table 1. Laboratory Variables Measured in the Collected Blood, Processed Blood, and in Patients' Blood Before and After Autotransfusion During Orthotopic Liver Transplantation (n = 14)

Measured variables (normal range)	Collected blood	Processed blood	Before IAT	After IAT
Na (136–146 mmol/L)	145 ± 7	138 ± 6[a]	138 ± 4	141 ± 8
K (3.5–5.5 mmol/L)	5.2 ± 1.0	3.8 ± 1.3[a]	4.2 ± 1.0	4.5 ± 1.0
Plasma hemoglobin (1–4 mg/dL)	678 ± 332	264 ± 127[a]	32 ± 12	40 ± 17
Ca^{2+} (0.9–1.2 mmol/L)	0.04 ± 0.04	0.20 ± 0.12[a]	1.0 ± 0.21	1.05 ± 0.14
Citrate (0.06–0.4 mmol/L)	2.9 ± 0.1	2.3 ± 0.8[a]	1.1 ± 0.8	1.0 ± 0.8
Bilirubin (0.3–1.5 mg/dL)	7.3 ± 8.6	0.6 ± 0.7[a]	8.4 ± 6.0	9.2 ± 6.5
Hematocrit (35%–50%)	19 ± 5	46 ± 4[a]	28 ± 6	31 ± 6
I (200–400 mg/dL)	21 ± 30	9 ± 9[a]	179 ± 91	158 ± 96
II (0.5–1.5 U/mL)	0.11 ± 0.08	0.04 ± 0.05[a]	0.32 ± 0.14	0.35 ± 0.11
VIII (0.5–1.5 U/mL)	1.12 ± 0.95	0.06 ± 0.09[a]	0.91 ± 0.58	1.00 ± 0.47
Platelet count (150–400 [$\times 10^3/mm^3$])	157 ± 95	22 ± 14[a]	66 ± 24	76 ± 24
Prothrombin time (10.5–13 s)	>100	>100	16.4 ± 2.2	16.5 ± 2.9
Activated partial thromboplastin time (25–34 s)	>150	>150	57.6 ± 29.7	57.7 ± 30.0
Thrombin time (11–17 s)	53.2 ± 15.6	58.0 ± 9.3	32.0 ± 17.6	26.5 ± 7.3
Reptilase time (13–18.5 s)	53.2 ± 15.7	58.4 ± 8.2	31.1 ± 12.2	28.5 ± 11.4
Reaction time (6–8 min)	>100	>100	7.0 ± 3.3	6.6 ± 2.6
Coagulation time (10–12 min)	>100	>100	14.5 ± 4.5	14.3 ± 4.8
Maximum amplitude (50–70 mm)	0	0	57 ± 32	63 ± 34
Clot formation rate (>50°)	0	0	31 ± 12	37 ± 11
Whole blood clot lysis index (>80%)	—	—	80 ± 33	76 ± 36

IAT, intraoperative autotransfusion.
Values are mean ± SD.
[a] $P < 0.05$ compared with the corresponding values of collected blood. No difference was found in measured variables before and after autotransfusion.

ville, Md.) for aerobic and anaerobic culture. The numbers of colonies present on the plates from each positive blood culture were noted. Bacterial cultures were also taken from the abdominal skin, peritoneal cavity, and bile duct stump using swabs. To obtain a culture from the air, a sheep blood agar plate was placed inside a mock cardiotomy reservoir, and the reservoir was connected to a vacuum to simulate the air volume that passes through the blood-collecting cardiotomy reservoir.

Postoperative observation. Postoperatively, levels of blood urea nitrogen and creatinine, urine output, and bacterial cultures were recorded in all patients in phases 1 and 2 for 7 days to identify clinical signs of renal dysfunction and infection.

Data analysis. The data are presented as mean ± SD. They were analyzed using analysis of variance of repeated measures, and specific differences were assessed with the Student-Newman-Keuls test. $P < 0.05$ was considered to be statistically significant.

Results

Phase 1

The mean volume of blood products transfused during surgery was 951 ± 826 mL of autotransfused blood, 8.9 ± 10.7 U of homologous RBC, 5.8 ± 5.7 U of whole blood, 9.6 ± 13.1 U of fresh frozen plasma, 13.2 ± 12.3 U of platelets, and 4.6 ± 6.3 U of cryoprecipitate, excluding one patient who received 32 L of the processed blood and 250 U of RBC. Biochemical, hematologic, and coagulation properties of the collected blood and the processed blood and the effects of IAT on recipients are summarized in Table 1. The high serum potassium level in the collected blood (5.24 ± 1.02 mmol/L) decreased after washing to 3.8 ± 1.3 mmol/L. Plasma free hemoglobin level was high in the collected blood (678 ± 332 mg/dL), and decreased by two-thirds after washing (264 ± 127 mg/dL). Serum citrate and bilirubin level decreased after washing, whereas serum ionized calcium level increased somewhat. On peripheral blood smears, slight to moderate elliptocytosis, a few poikilocytes and keratinocytes, and occasional RBC fragments were seen in both the collected blood and the processed blood. Few white blood cells and platelets were present in the collected blood, and platelets were rarely seen in the processed blood.

Intraoperative autotransfusion (500 mL) did not alter serum levels of sodium, potassium, ionized calcium, citrate, and bilirubin in the patients' blood. A change in plasma free hemoglobin level after IAT (from 32.4 ± 12.0 to 40.4 ± 17.2 mg/dL) was not statistically significant. Mean plasma free hemoglobin

Table 2. Incidence of Positive and Negative Bacterial Cultures in Semiquantitative Bacteriologic Study (phase 1, $n = 14$)

	Aerobes		Anaerobes	
	Positive	Negative	Positive	Negative
Collected blood	4	10	5	9
Processed blood	6	8	2	12
Before autotransfusion	0	14	0	14
After autotransfusion	0	14	0	14

Bacterial count was rare in all positive cultures.

Table 3. Organisms Grown in Quantitative Bacteriologic Study (phase 2, $n = 11$)

Patient	Skin	Peritoneal cavity	Bile duct stump	Collected blood	Processed blood	Blood of recipient	Air
1–6	—	—	—	—	—	—	—
7	S	—	—	—	S	—	—
8	S	—	—	—	—	—	—
9	—	—	—		S	—	S,B
10	—	—	—	—	S	—	S
11	—	—	—	—	—	—	S

S, coagulase (-) *Staphylococcus epidermidis*; B, *Bacillus* sp.

level measured at the end of surgery in 10 patients was 42.3 ± 15.8 mg/dL (range, 18–63 mg/dL). A low hematocrit in the collected blood (19.0 vol%) was increased to 46.2 vol% after processing; IAT did not affect the hematocrit in patients' blood. Red blood cell morphology was within the normal range before and after IAT in all instances.

Levels of all coagulation factors (I, II, and VIII) and platelet count were low in the collected blood, and they decreased further after washing. All measurements of prothrombin time and activated partial thromboplastin time were greater than 100 s and 150 s, respectively. Euglobulin lysis time could not be determined because no clot formation occurred in the collected blood or processed blood. A moderate level of fibrin monomer (determined by ethanol-gel test) was detected in four collected blood samples, and FDP were detected in seven. They were moderately positive in one sample each after washing. Thrombelastography produced a straight line from all samples of the collected blood and the processed blood, indicating absence of clot formation (Table 1). Intraoperative autotransfusion did not alter serum levels of coagulation factors. The numbers of patients with euglobulin lysis time less than 120 min, presence of fibrin monomers, and presence of FDP remained unchanged after IAT: 6, 5, and 3, respectively. Intraoperative autotransfusion did not change coagulation function as demonstrated by the following thrombelastographic variables: function of coagulation factors, by reaction time and coagulation time; function of fibrinogen, by clot formation rate; platelet function, by maximum amplitude; and fibrinolytic activity by whole blood clot lysis index; and, fibrinolysis time (2). Fibrinolysis time was less than 120 min in one patient before and after IAT.

Cultures taken from the collected blood were positive for aerobes in four and for anaerobes in five patients; the cultures were positive after washing for aerobes in six and for anaerobes in two patients (Table 2). All positive cultures showed occasional to rare coagulase (-) *Staphylococcus epidermidis*. All blood cultures taken from the patients before and after IAT were sterile.

Phase 2

Four of 15 patients were excluded from the analysis. Two had insufficient data and two met the exclusion criteria, one with unexpected spontaneous bacterial peritonitis and one with inadvertent surgical entrance of the gastrointestinal tract. In all of the other 11 patients, the peritoneal cavity, bile duct stump, collected blood, and patient's blood were sterile (Table 3). Bacterial cultures from all sites were negative in six patients. Of the remaining five patients, skin cultures were positive for coagulase (-) *Staphylococcus* in two patients, the processed blood was positive for coagulase (-) *Staphylococcus* in three, and air was positive for coagulase (-) *Staphylococcus* or *Bacillus* sp in three. One of the three patients whose processed blood contained coagulase (-) *Staphylococcus* had the same bacteria on the skin, and two of them had the same bacteria in the culture of air from the mock reservoir. The bacterial count was rare (<2 colonies) in all processed blood samples. The number of colonies found in air was 2, 2, and 6 of coagulase (-) *Staphylococcus epidermidis* and 12 of *Bacillus* sp. The two patients with grossly contaminated peritoneal cavities who were excluded from the study showed a large quantity of *Pseudomonas aeruginosa*, *Streptococcus fecalis*, and *Escherichia coli* in the peritoneal cavity, the collected blood, and the processed blood.

Postoperative Findings

The postoperative renal function of the patients in phase 1, who received IAT, and those in phase 2, who did not, is shown in Table 4. Blood urea nitrogen and the serum creatinine level gradually increased in the postoperative period, and no difference was able 4. Postoperative Renal Function of Patients Who Received Intraoperative Autotransfusion (phase 1 study, $n = 14$) nd Who Did Not Receive Intraoperative Autotransfusion (phase 2 study, $n = 11$)

	Before surgery	POD 1	POD 3	POD 5	POD 7
atients with IAT					
BUN (mg/dL)	23.0 ± 25.2	24.5 ± 9.7	45.5 ± 17.4	59.6 ± 27.3	52.5 ± 45.4
Creatinine (mg/dL)	1.3 ± 0.8	1.8 ± 1.6	2.3 ± 1.3	2.2 ± 1.7	1.7 ± 1.0
Urine output (L/24 h)		3.8 ± 4.1	2.9 ± 1.1	3.2 ± 1.5	2.4 ± 1.0
atients without IAT					
BUN (mg/dL)	16.3 ± 10.2	22.4 ± 8.0	34.0 ± 14.4	45.5 ± 25.2	43.2 ± 29.2
Creatinine (mg/dL)	1.0 ± 0.5	0.8 ± 0.3	1.5 ± 0.9	1.6 ± 1.0	1.4 ± 0.8
Urine output (L/24 h)		3.0 ± 1.2	4.3 ± 1.3	3.2 ± 1.5	2.8 ± 2.1

POD, postoperative day; BUN, blood urea nitrogen.
No difference was found between the two groups of patients.

ound between the two groups of patients. Blood ultures were sterile for 1 wk postoperatively in all atients with or without IAT. One patient who reeived IAT had *Escherichia coli* in a urine sample. In ree patients without IAT, *Candida glabrata*, *Candida lbicans*, *Streptococcus faecium*, coagulase (-) *Staphyloccus*, or diphtheroids were found in the sputum, ile duct, or drain site.

iscussion

he percentage of total transfused RBC provided by AT in this study (15%–20%) was less than that eported by others (40%–60%) (12,16). Only one atheter was used in this study because recovery olume was not the focus of study and because, to void contamination, IAT began after drainage of scites and terminated before biliary tract reconstrucon. In this study, only acute effects of IAT on ecipients were studied after transfusion of 500 mL of rocessed blood because the physiologic changes that ormally occur during liver transplantation could verwhelm the effects of IAT.

Intraoperative autotransfusion has been used durg OLT in several centers without documented comlications (16–18). Dzik and Jenkins reported that no omplication was seen even in patients who received nwashed blood (17). Nonetheless, coagulopathy, fection, electrolyte imbalance, and renal dysfuncon associated with IAT may interfere with the erioperative course of liver transplant recipients.

Hemolysis occurs during the collection phase of AT because of turbulence of the blood and air terface (19–21). Intraoperative autotransfusion of emolyzed blood may lead to hyperkalemia (22), and BC stroma may precipitate disseminated intravascur coagulation or renal dysfunction. However, most f the plasma free hemoglobin, potassium, and a moderate number of fragmented RBCs in the collected blood were removed during the wash cycle in this study. In healthy subjects, haptoglobin binds with up to 100 mg/dL of hemoglobin, and hemoglobinuria occurs when the binding capacity of haptoglobin is exhausted. Haptoglobin level is known to be lower after IAT and to return toward the normal range within 24 h (23). Although a high plasma free hemoglobin level has been suggested as a cause of renal dysfunction by deposition of hematin in the renal tubule, renal insufficiency now appears to be caused by deposition of RBC stroma (24). The rare observation of RBC fragments, clinically acceptable level of plasma free hemoglobin, and relatively unperturbed postoperative renal function in this study and others suggest that hemolysis-related renal dysfunction is not a clinical concern (18).

Anticoagulation is required during the blood collection phase to prevent clot formation, although the blood in the serous cavity is frequently defibrinated (25,26). Acid-citrate-dextrose solution was used in this study because monitoring and reversal of this anticoagulant are easier and more predictable than those of heparin. The dose of ACD used in this study (6–12 mL/min) appears to be satisfactory, as evidenced by a very low Ca^{2+} level in the collected blood, prolonged prothrombin time and activated partial thromboplastin time, and no adverse effect on coagulation after IAT. By contrast, when heparin is used for anticoagulation, the residual heparin level can be as high as three times the permissible dose (8), and its effect may be difficult to treat in patients with liver disease.

As expected, the levels of coagulation factors were low and the presence of FDP was detected in the collected blood, caused by a defibrination effect (25). The effects of IAT on coagulation appear to be negligible: the levels of coagulation factors and FDP, platelet count, and blood coagulability determined by thrombelastography remained unchanged after IAT. The presence of FDP and the moderate fibrinolysis seen in some patients were most likely due to primary fibrinolysis, a common occurrence during OLT (3). It has been suggested that IAT is associated with disseminated intravascular coagulation, resulting from the administration of FDP, fragmented RBC, tissue thromboplastin, and activated plasmin, particularly when the IAT system does not include a wash phase. Lawrence-Brown et al. reported that the level of D-Dimers which interfere with platelet aggregation and fibrin polymerization was 85 times the normal value in the collected blood but decreased to within the normal range after washing (19). This suggests that disseminated intravascular coagulation does not play a major role when IAT incorporates a wash phase.

In this study, a balanced salt solution (Plasma-Lyte-A) was used for washing to preserve electrolyte balance. Normal saline is a better choice, however, when hyperkalemia ($K > 5.0$ mEq/L) is a concern because washing with normal saline reduces the potassium level to less than 2 mEq/L. The wash phase effectively reduces the degree of contaminants such as bile juice, tissue, certain medications, and bacteria. In an animal study, transfusion of blood contaminated with feces, bile, body fat, splenic tissue, and liver tissue did not affect survival (27), and in patients outcome was not complicated by use of IAT during surgery of the serous cavities (28). Patients who had malignancy were excluded from our study because tumor cells have been found in processed blood even after using filters (29), although it is unclear whether such tumor cells are viable (30). Also, patients with hepatitis antigen seropositivity were excluded from the study in an attempt to reduce the chance of recurrent antigenemia. Microaggregates are not likely to cause clinical problems, because a 40-μm filter removes 92% of microaggregates and because animals that received IAT of four times the blood volume developed no pulmonary dysfunction (31). Washing was shown to be effective in removing residual neomycin and bacitracin (32), but inadequate washout of catecholamines was reported to cause a hypertensive reaction in a patient with pheochromocytoma (33).

Bacterial contamination is a particular concern in immunosuppressed organ recipients. In phase 1 of this study, 9 of 30 samples of the collected blood were positive for coagulase (-) *Staphylococcus epidermidis*. This bacterial contamination is not surprising because blood collected during cardiac surgery contained similar bacteria (34,35). The presence of bacteria in the processed blood samples may be the result of inadequate washout of bacteria, but about 5% of bacteria has been shown to remain even after washing with 10 L of fluid (36). The source and number of bacteria grown in phase 2 of this study are interesting. In four patients whose processed blood was positive for coagulase (-) *Staphylococcus epidermidis*, the same bacteria were isolated from skin or air culture. Hence, the source of contamination is most likely environmental and not enteric. It was not surprising to observe a heavy growth of clinically significant pathogenic bacteria in the two patients who were excluded from the study because of gross evidence of infection.

Although the relation between the presence of bacteria in autotransfused blood and clinical infection is unclear, IAT-related infection appears to be uncommon in both animals and humans. Glover et al. showed that animals transfused with blood contaminated with intestinal contents did show transient bacteremia but developed no clinical complications (37). Smith et al. allowed dogs to shed various volumes of blood and returned the unwashed blood with or without enteric contamination (38). Animals that received contaminated blood alone had greater mortality, but those transfused with contaminated blood plus antibiotics (penicillin and streptomycin) had equivalent mortality to that of animals given uncontaminated blood. In a series of six patients with abdominal trauma who had IAT, three received blood with enteric contamination; the blood culture was positive postoperatively in only one of the three, a patient with multiple organ failure (39). Timberlake and McSwain observed superficial wound infection in only 1 of 11 patients contaminated with enteric organisms and concluded that there is little evidence to confirm the fear of inducing sepsis with contaminated blood (40). Our findings are similar. The bacterial counts in this study were all rare, and the blood cultures of patients before and after IAT and during the 1-wk postoperative period were all sterile, suggesting that bacteria were too few to cause infection in patients who received prophylactic broad-spectrum antibiotics.

In summary, the biochemical and hematologic quality of blood prepared by an autotransfusion system (Cell Saver #4, Haemonetics Inc.) using ACD as an anticoagulant is clinically acceptable during liver transplantation. Bacterial contamination was found in one-third of cases, apparently from the skin or room air, but the quantity of the bacteria was too small to cause infection in patients receiving prophylactic antibiotic therapy. Intraoperative autotransfusion should be avoided, however, in patients with a source of infection in the peritoneal cavity.

The authors thank Haemonetics Inc. (Braintree, Mass.) for their support, Steven Miller and Mary-Jo Dimasi for technical assistance, Drs. Stephen J. Dummer, Glenn Ramsey, Thomas E. Starzl, and Richard L. Simmons for their criticism, and Lisa Cohn for her editorial help.

References

1. Bontempo FA, Lewis JH, Van Thiel DH, et al. The relation of preoperative coagulation findings to diagnosis, blood usage, and survival in adult liver transplantation. Transplantation 1985;39:532–6.
2. Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985;64:888–96.
3. Kang Y, Lewis JH, Navalgund A, et al. Epsilon-aminocaproic acid for treatment of fibrinolysis during liver transplantation. Anesthesiology 1987;66:766–73.
4. Shaw BW Jr, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg 1984;200:524–34.
5. Kang Y, Aggarwal S, Freeman JA. Update on anesthesia for adult liver transplantation. Transplant Proc 1987;19(Suppl 3): 7–12.
6. Ellison N, Wurzel HA. Editorial: the blood shortage: is autotransfusion an answer? Anesthesiology 1975;43:288–90.
7. Ray JM, Flynn JC, Bierman AH. Erythrocyte survival following intraoperative autotransfusion in spinal injury: an in vivo comparative study and 5-year update. Spine 1986;11:879–82.
8. McShane AJ, Power C, Jackson JF, et al. Autotransfusion: quality of blood prepared with a red cell processing device. Br J Anaesth 1987;59:1035–9.
9. Kusne S, Dummer JS, Singh N, et al. Infections after liver transplantation. An analysis of 101 consecutive cases. Medicine (Baltimore) 1988;67:132–43.
0. Weber T, Marino IR, Kang YG, Esquivel CD, Starzl TE, Duquesnoy RJ. Intraoperative blood transfusions in highly alloimmunized patients undergoing orthotopic liver transplantation. Transplantation 1989;47:797–801.
1. Breyer RH, Engelman RM, Rousou JA, Lemeshow S. Blood conservation for myocardial revascularization. Is it cost effective? J Thorac Cardiovasc Surg 1987;93:512–22.
2. Goulet JA, Bray TJ, Timmerman LA, Benson DR, Bargar WL. Intraoperative autologous transfusion in orthopaedic patients. J Bone Joint Surg [Am] 1989;71:3–8.
3. Keeling MM, Gray LA Jr, Brink MA, Hillerich VK, Bland KI. Intraoperative autotransfusion: experience in 725 consecutive cases. Ann Surg 1983;197:536–41.
4. Reul GJ, Solis RT, Greenberg SD, Mattox KL, Whisennand HH. Experience with autotransfusion in the surgical management of trauma. Surgery 1974;76:546–55.
5. Jacobs LM, Hsieh JW. A clinical review of autotransfusion and its role in trauma. JAMA 1984;251:3283–7.
6. Lindop MJ, Farman JV, Smith MF. Anaesthesia: assessment and intraoperative management. In: Calne RY, ed. Liver transplantation. London: Grune & Stratton, 1983:128–9.
7. Dzik WH, Jenkins R. Use of intraoperative blood salvage during orthotopic liver transplantation. Arch Surg 1985;120: 946–8.
8. Van Voorst SJ, Peters TG, Williams JW, Vera SR, Britt LG. Autotransfusion in hepatic transplantation. Am Surg 1985;51: 623–6.
19. Lawrence-Brown MM, Couch C, Halliday M, Hellings M, Barr A, Marshall L. D-dimer levels in blood salvage for autotransfusion. Aust NZ J Surg 1989;59:67–70.
20. Aaron RK, Beazley RM, Riggle GC. Hematologic integrity after intraoperative allotransfusion. Arch Surg 1974;108:831–7.
21. Paravicini D, Wasylewski AH, Rassat J, Thys J. Red blood cell survival and morphology during and after intraoperative autotransfusion. Acta Anaesthesiol Belg 1984;35(Suppl):43–9.
22. Young LE. Complications of blood transfusion. Ann Intern Med 1964;61:136.
23. Henn A, Hoffmann R, Muller HA. Haptoglobin determination in the serum of patients following intraoperative autotransfusion using Haemonetics Cell Saver III. Studies on the loading of patients with free hemoglobin in retransfused erythrocyte concentrate. Anaesthetist 1988;37:741–5.
24. Rabiner SF, Helbert JR, Lopas H, Friedman LH. Evaluation of a stroma-free hemoglobin solution for use as a plasma expander. J Exp Med 1967;126:1127–42.
25. Hartz RS, Smith JA, Green D. Autotransfusion after cardiac operation. Assessment of hemostatic factors. J Thorac Cardiovasc Surg 1988;96:178–82.
26. Rakower SR. Blood surface interactions in extravascular salvageable blood pools. Surg Gynecol Obstet 1977;145:555–8.
27. Klebanoff G. Early clinical experience with a disposable unit for the intraoperative salvage and reinfusion of blood loss (intraoperative autotransfusion). Am J Surg 1970;120:718–22.
28. Griswold RA, Ortner AB. The use of autotransfusion in surgery of the serous cavities. Surg Gynecol Obstet 1943;77:167–71.
29. Homann B, Zenner HP, Schauber J, Ackermann R. Tumor cells carried through autotransfusion. Are these cells still malignant? Acta Anaesthesiol Belg 1984;35(Suppl):51–9.
30. Yaw PB, Sentany M, Link WJ, Wahle WM, Glover JL. Tumor cells carried through autotransfusion. Contraindication to intraoperative blood recovery? JAMA 1975;231:490–1.
31. Wright CB, Solis RT. Microaggregation in canine autotransfusion. Am J Surg 1973;126:25–9.
32. Paravicini D, Thys J, Hein H. Use of neomycin-bacitracin irrigating solution with intraoperative autotransfusions during orthopedic operations. Arzneimittelforschung 1983;33:997–9.
33. Smith DF, Mihm FG, Mefford I. Hypertension after intraoperative autotransfusion in bilateral adrenalectomy for pheochromocytoma. Anesthesiology 1983;58:182–4.
34. Thurer RL, Lytle BW, Cosgrove DM, Loop FD. Autotransfusion following cardiac operations: a randomized, prospective study. Ann Thorac Surg 1979;27:500–7.
35. Cosgrove DM, Amiot DM, Meserko JJ. An improved technique for autotransfusion of shed mediastinal blood. Ann Thorac Surg 1985;40:519–20.
36. Boudreaux JP, Bornside GH, Cohn I Jr. Emergency autotransfusion: partial cleansing of bacteria-laden blood by cell washing. J Trauma 1983;23:31–5.
37. Glover JL, Smith R, Yaw PB, Radigan LR, Bendick P, Plawecki R. Autotransfusion of blood contaminated by intestinal contents. J Am Coll Emergency Physicians 1978;7:142–4.
38. Smith RN, Yaw PB, Glover JL. Autotransfusion of contaminated intraperitoneal blood: an experimental study. J Trauma 1978;18:341–4.
39. Jurkovich GJ, Moore EE, Medina G. Autotransfusion in trauma. A pragmatic analysis. Am J Surg 1984;148:782–5.
40. Timberlake GA, McSwain NE Jr. Autotransfusion of blood contaminated by enteric contents: a potentially life-saving measure in the massively hemorrhaging trauma patient? J Trauma 1988;28:855–7.

ANESTH ANALG 1991;72:101-4

Amino Acids Fail to Prevent Halothane Depression of Albumin Synthesis: Studies in the Isolated Perfused Rat Liver

Jonathan B. Kruskal, MB, ChB, PhD, John J. Franks, MD, and Ralph E. Kirsch, MD

KRUSKAL JB, FRANKS JJ, KIRSCH RE. Amino acids fail to prevent halothane depression of albumin synthesis: studies in the isolated perfused rat liver. Anesth Analg 1991;72:101-4.

Halothane (1.3 MAC) and ethanol (0.4%) depress albumin synthesis in isolated perfused rat livers (IPRLs). Addition of amino acids prevents depression by ethanol. We have examined the effects of amino acids on albumin synthesis by IPRLs exposed to halothane. Seventeen livers were perfused with a mixture of rat erythrocytes and rabbit plasma. Five were exposed to oxygen/carbon dioxide alone and 12 to oxygen/carbon dioxide with 1.5% halothane. A mixture of 10 essential amino acids was added to the perfusate of six of the halothane-exposed livers to a concentration approximately 10 times the normal rat plasma level. Perfusate concentrations of newly synthesized albumin were measured by radial immunodiffusion, and the rate of synthesis for the 4.25-h study period was calculated. The mean ± SEM albumin synthetic rate (mg/h per 300-g rat) in the control group (12.13 ± 1.36) was significantly greater than in the group receiving halothane alone (6.98 ± 0.92). Amino acid treatment failed to prevent halothane depression of albumin synthesis (8.68 ± 0.84). Thus, although amino acids block ethanol depression of albumin synthesis, we could show no such effect in rat livers exposed to halothane.

Key Words: ANESTHETICS, VOLATILE—halothane. LIVER, METABOLISM—albumin.

We have demonstrated (a) that isolated perfused rat livers (IPRLs) exposed to 1.5% halothane (1.3 MAC) in a mixture of oxygen (O_2) and carbon dioxide (CO_2) (95%/5%) or to O_2/CO_2 alone produce urea, albumin, and transferrin at constant rates during a 4.25-h perfusion, and (b) that halothane depresses albumin and transferrin synthesis by nearly one-half without disturbing urea production (1).

Essential amino acids stimulate albumin synthesis in the protein-depleted rat (2,3) and also protect the IPRL from the inhibitory effects of ethanol on albumin synthesis (4). The role of amino acids in the prevention of halothane depression of albumin synthesis has not been studied. We therefore looked for possible beneficial effects of amino acid treatment on albumin synthesis by IPRLs exposed to a clinically relevant concentration of halothane.

Materials and Methods

Animals

Animal use was approved by the Ethics and Research Committee of the Faculty of Medicine of the University of Cape Town. Male Black-Hooded rats of the Long Evans strain, weighing 290–304 g, housed under controlled conditions of temperature and humidity, and allowed access to food and water ad libitum, were used as liver and red cell donors. Male New Zealand White rabbits, maintained under the same conditions, were used as plasma donors.

Liver Perfusion

Seventeen livers were perfused ex situ, as described previously (1), with a heterologous mixture of heparinized rabbit plasma and rat erythrocytes washed

---

Supported by the South African Medical Research Council and, in part, by the Study Center for Anesthesia Toxicology, Vanderbilt University, Nashville, Tennessee.

Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 1988.

Received from the UCT/MRC Liver Research Center, University of Cape Town Medical School, Observatory 7925, Cape Town, South Africa; and the Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, Tennessee. Accepted for publication August 27, 1990.

Address correspondence to Dr. Franks, Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, TN 37232.

©1991 by the International Anesthesia Research Society

twice with 0.9% sodium chloride. The proportions of plasma and red cells were adjusted to obtain a hematocrit of 25%–29%. The perfusate was exposed to O_2/CO_2 (95%/5%) by circulation in a warmed (37°C), humidified perfusion cabinet for 0.5 h before insertion of the liver and throughout a 4.25-h period of liver perfusion. Before placement in the perfusion chamber, each liver was flushed with isotonic crystalloid (Plasma-Lyte A, Travenol, Deerfield, Ill.) for 2 min at a pressure of no more than 15 cm H_2O. The perfusion mixture was then pumped antegrade through the portal vein, with pressure maintained at 12–13 cm H_2O. Perfusate hematocrit, flow rate, and the partial pressures of O_2 and CO_2, as well as the rate of bile production, were monitored. Five livers were exposed to O_2/CO_2 (95%/5%) alone and 12 to O_2/CO_2 and 1.5% halothane (1.3 MAC). Six of the halothane-exposed IPRLs were perfused with a plasma/red cell mixture to which had been added 10 essential amino acids, each to a concentration approximately 10 times the normal rat plasma level (4). In this group, liver donor rats also received a similar amino acid mixture intragastrically. This solution was dissolved in 2.0 mL of sterile water and given 1 h preoperatively.

The amino acid mixtures consisted of L-isomers of arginine, asparagine, isoleucine, lysine, methionine, phenylalanine, proline, threonine, tryptophan, and valine. The amounts given have previously been shown to correct albumin synthesis in protein malnutrition (3) and alcohol exposure (4).

Perfusate rat albumin concentration was determined by radial immunodiffusion (5). The antisera used (Cooper Diagnostics, Malvern, Pa.) reacted with rat but not with rabbit albumin. Perfusate samples for the measurement of albumin and urea were taken before cannulation of the liver and 0.25, 0.75, 1.25, 1.75, 2.25, 2.75, 3.25, and 4.25 h after the start of liver perfusion. Urea and albumin synthetic rates were estimated by linear regression analysis of accumulated values over time, with rates taken as equal to the slopes of the fitted lines (1). Corrections were made for perfusate volume changes due to sample removal. Synthetic rates for the 4.25-h perfusion period were expressed as milligrams per hour per 300-g rat. Results in the control (C), halothane (H)-, and halothane with amino acid (HA)-treated groups were compared by one-way analysis of variance and by Duncan's multiple range comparison procedure (6). Significant differences among means were inferred if P was less than 0.05.

Upon completion of perfusions, central portions of livers were fixed in formalin, and paraffin sections were subsequently stained with hematoxylin and eosin. Sections were examined by a pathologist without knowledge of experimental treatment.

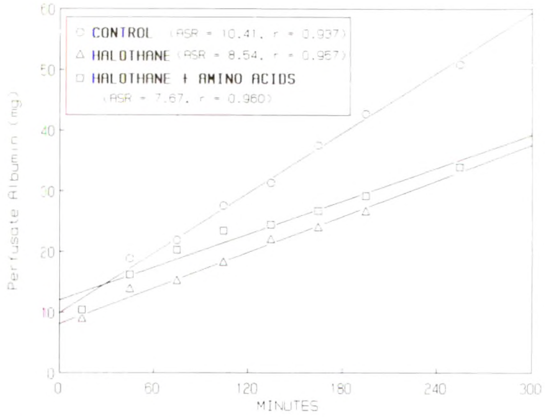


Figure 1. Albumin synthetic rates (ASR) of representative IPRLs exposed to O_2/CO_2 alone or to 1.5% halothane with and without amino acid supplementation. Data points for each liver represent the total amount of perfusate albumin less preperfusion values. Albumin synthetic rates are derived from the slope of each regression line and expressed per 300-g rat.

Results

Perfusate flow rates ranged from 1.9 to 3.6, 1.6 to 3.4, and 1.8 to 3.7 $mL \cdot min^{-1} \cdot g\ liver^{-1}$ in C, H, and HA livers, respectively. Bile excretion ranged from 1.3 to 1.9, 1.1 to 1.6, and 1.1 to 1.5 $\mu L \cdot min^{-1}\ g\ liver^{-1}$ in C, H, and HA livers. No differences in perfusate flow or bile production were noted among groups, nor were differences seen in other criteria for perfused liver viability including perfusate packed cell volume, pH, oxygen saturation, and partial pressures of O_2 and CO_2. Sinusoidal dilatation was the only histologic change noted after perfusion, with no differences in degree noted among the three treatment groups. No nuclear or cytoplasmic abnormalities, including vacuolization, were seen in any treatment group.

Figure 1 shows plots of albumin synthesis by representative C, H, and HA livers. A constant rate of production was found throughout the course of each liver perfusion. Protein synthetic rates, expressed as milligrams per hour per 300-g rat, are shown in Table 1. Values are given as mean ± SEM for each treatment group. Both groups receiving halothane produced significantly less albumin than the control group. No significant difference was detected between the two halothane groups.

Urea production (mean ± SEM) was 8.72 ± 0.98, 9.64 ± 0.91, and 40.0 ± 1.71 mg/h per 300-g rat in C, H, and HA livers, respectively (Table 1). The mean urea synthetic rates in C and H livers did not differ

Table 1. Albumin Synthetic Rates and Urea Synthetic Rates in Control, Halothane-, and Halothane With Amino Acid-Treated Isolated Perfused Rat Livers

	Control ($n = 5$)	Halothane ($n = 6$)	Halothane + amino acids ($n = 6$)
ASR (mg/h per 300-g rat)	12.13 ± 1.36	6.98 ± 0.92[a]	8.68 ± 0.84[a]
USR (mg/h per 300-g rat)	8.72 ± 0.98	9.64 ± 0.91	40.0 ± 1.71[a]

ASR, albumin synthetic rates; USR, urea synthetic rates.
All values are expressed as mean ± SEM.
[a] Differs significantly from control ($P < 0.05$).

significantly. Livers treated with amino acids synthesized significantly increased amounts of urea. A constant rate of urea production over 4.25 h was a characteristic finding in all experiments, with and without halothane exposure.

Discussion

Proteins synthesized and secreted by the liver play important roles in hemostasis and osmotic homeostasis, in the transport of xenobiotics and essential trace elements, and in immunologic surveillance. Inhibition of hepatic protein synthesis as a consequence of anesthetic and surgical intervention could disturb some of these functions and complicate postoperative recovery, especially in patients in poor nutritional status. Methods of preventing this inhibition might be useful in such individuals.

Diminished protein synthesis in perfused rat livers (7) and in isolated rat hepatocytes (8) has been observed when these preparations were exposed to halothane. Heys et al. (9) reported significant depression of liver tissue protein synthesis in rats exposed to halothane, pentothal, or a nitrous oxide/halothane mixture. We have recently shown that halothane, enflurane, isoflurane, and sevoflurane (10) significantly reduce synthesis of albumin, transferrin, and fibrinogen by the IPRL. These various studies suggest that halothane may be a general depressant of hepatic protein synthesis. Because adding a mixture of essential amino acids to the perfusate can prevent or reverse ethanol-induced depression of albumin synthesis in the IPRL (4), we examined the effect of amino acids on albumin synthesis in halothane-treated livers.

Mean albumin synthetic rates in the control and halothane-treated IPRLs were 12.12 and 6.98 mg/h per 300-g rat, values very similar to those we reported previously (1). The albumin synthetic rate in livers exposed to halothane but also treated with amino acids averaged 8.68 mg/h per 300-g rat, a value different from controls but not significantly different from livers treated only with halothane. As noted before (1,10), we found that perfused livers synthesized albumin and urea at constant rates, indicating that hepatic functional integrity is reasonably well maintained during a 4-h perfusion. Lack of an effect on urea synthesis by halothane suggests that this anesthetic agent does not cause a general depression of hepatic biochemical processes. The marked increase in urea production after amino acid treatment has been observed before (4), and reflects deamination of exogenous substrate. The failure of an amino acid mixture to prevent halothane-induced depression of albumin synthesis suggests that differences exist in the molecular mechanisms of depression by ethanol and halothane.

Hepatic secretory proteins, such as albumin and fibrinogen, are necessary for normal host resistance and tissue repair after surgery (11). Anesthetic agents that decrease the levels of these proteins might thus complicate postoperative recovery, particularly in the malnourished patient. Our results suggest that preoperative measures such as administering amino acids parenterally would not prevent depression of albumin synthesis by halothane and thus, by implication, might be unlikely to maintain normal synthesis of other proteins in the liver exposed to halothane.

The authors thank M. Parker, L. Frith, and V. Hancock for technical assistance.

References

1. Franks JJ, Kruskal JB, Kirsch RE, Beechey APG, Morrell DF, Harrison GG. Halothane decreases albumin and transferrin synthesis: studies in the isolated, perfused rat liver and in the intact rat. Anesthesiology 1988;68:529–33.
2. Kirsch R, Frith L, Black E, Hoffenberg R. Regulation of albumin synthesis and catabolism by alteration of dietary protein. Nature 1968;217:578–9.
3. Kelman L, Saunders SJ, Wicht S, et al. The effects of amino acids on albumin synthesis by the isolated perfused rat liver. Biochem J 1972;129:805–9.
4. Kirsch RE, Frith LO'C, Stead RH, Saunders SJ. Effect of alcohol on albumin synthesis by the isolated perfused rat liver. Am J Clin Nutr 1973;26:1191–4.
5. Mancini G, Carbonara AO, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. Immunochemistry 1965;2:235–54.
6. Dowdy S, Wearden S. Statistics for research. New York: John Wiley & Sons, 1983.

7. Flaim KE, Jefferson LS, McGwire JB, Rannels DE. Effect of halothane on synthesis and secretion of liver proteins. Mol Pharmacol 1983;24:277–81.

8. Aune H, Bessesen A, Olsen H, Morland J. Acute effects of halothane and enflurane on drug metabolism and protein synthesis in isolated hepatocytes. Acta Pharmacol Toxicol (Copenhagen) 1983;53:363–8.

9. Heys SD, Norton AC, Dundas CR, Eremin O, Ferguson K, Garlick PJ. Anaesthetic agents and their effect on tissue protein synthesis in the rat. Clin Sci 1989;77:651–5.

10. Franks JJ, Kruskal JB, Holaday DA. Immediate depression of fibrinogen, albumin and transferrin synthesis by halothane, isoflurane, sevoflurane and enflurane. Anesthesiology 1989;71: A238.

11. Meakins JL, Pietsch JB, Bubenick O, et al. Delayed hypersensitivity: indicator of acquired failure of host defences in sepsis and trauma. Ann Surg 1977;186:241–50.

Interpleural Analgesia After Thoracotomy

F. Michael Ferrante, MD, Vincent W.S. Chan, MD, G. Richard Arthur, PhD, and Angelo G. Rocco, MD

FERRANTE FM, CHAN VWS, ARTHUR GR, ROCCO AG. Interpleural analgesia after thoracotomy. Anesth Analg 1991;72:105–9.

We examined the effects of the following variables on interpleural analgesia after thoracotomy: addition of epinephrine to local anesthetic, thoracostomy drainage, two-catheter placement, and location of catheter tips. Twenty patients were randomized to have one catheter (paravertebral tip location) or two catheters (paravertebral and lateral thoracic wall tip locations). Interpleural catheters were sutured to the parietal pleura by the surgeon at time of wound closure. Patients were then randomly assigned to receive 20 mL of 0.5% bupivacaine with 1:200,000 epinephrine through the single catheter or 10 mL of 0.5% bupivacaine with or without 1:200,000 epinephrine through each of the two catheters while supine. Bupivacaine concentrations in whole blood and in thoracostomy drainage fluid were assayed by gas chromatography. Actual content of bupivacaine in the drainage fluid was calculated. Degree of analgesia was assessed by verbal numerical pain scores over the first 4 h and opioid demand thereafter. Addition of epinephrine to bupivacaine did not influence the degree of analgesia. Approximately 30%–40% of any administered dose of bupivacaine was lost via the thoracostomy tube over a 4-h period. There was no correlation between the true initial dose (100 mg minus thoracostomy drainage) and C_{max}. *Use of two catheters resulted in significantly less opioid requirements after an initial 8-h period. Failure to achieve adequate interpleural analgesia in postthoracotomy patients may be related to loss of anesthetic via thoracostomy drainage, presence of extravasated blood and tissue fluid in the pleural space, and possibly sequestration and channeling of flow of local anesthetic by restricted motion of an operated lung. Use of multiple catheters may result in a more even distribution of local anesthetic over the pleura, which may improve quality of interpleural analgesia in postthoracotomy patients.*

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—interpleural. ANESTHETICS, LOCAL—bupivacaine. PAIN, POSTOPERATIVE.

Certain investigators have found the efficacy of interpleural analgesia to be disappointing for alleviation of postthoracotomy pain (1,2), whereas others have found the technique effective (3,4). This variability of analgesia is intellectually disquieting and may indicate either (a) nonfeasibility of the technique or (b) lack of understanding of the mechanism of analgesia or the optimal method of performance. This study attempted to examine the roles of epinephrine, thoracostomy drainage, and a double-catheter technique upon efficacy of interpleural analgesia after thoracotomy.

Methods

This study was approved by the institution's Committee for the Protection of Human Subjects From Research Risks. Written informed consent was obtained from 20 patients (9 men, 11 women) who were scheduled for elective thoracotomy. General anesthesia was performed using diazepam or midazolam as premedicant, with intravenous thiopental for induction and oxygen/nitrous oxide/muscle relaxant/opioid/volatile agent used for maintenance. Intraoperative opioid administration was not restricted. Thoracotomies were performed for open lung biopsy ($n = 1$), wedge resection ($n = 3$), lobectomy ($n = 15$), and pneumonectomy ($n = 1$). All incisions were made in the posterior fifth intercostal space. All thoracostomy tubes were positioned posteriorly in the pleural space.

Patients were divided into three study groups based on (a) number and location of interpleural catheters and (b) administration of bupivacaine with or without epinephrine (Table 1).

Received from the Pain Treatment Service and the Anesthesia Research Laboratories, Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication August 27, 1990.

Supported in part by a Biomedical Research Support Grant.

Address correspondence to Dr. Ferrante, Director, Pain Treatment Service, Department of Anesthesia, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

able 1. Group Designation According to Interpleural atheter Tip Location and Use of Epinephrine

Group esignation	Catheter	Interpleural catheter location	0.5% Bupivacaine +
E ($n = 7$)	Double	Paravertebral and lateral	+ 1:200,000 epinephrine
P ($n = 6$)	Double	Paravertebral and lateral	Plain (no epinephrine)
E ($n = 7$)	Single	Paravertebral	+ 1:200,000 epinephrine

(a) The surgeon randomly inserted one or two nterpleural catheters (20-gauge epidural catheters) ercutaneously via a Tuohy needle through the thoacic wall at time of wound closure. All catheter tips ere sutured loosely to the posterior parietal pleura. atheter tip locations were designated as *paravertebral* at the second or third intercostal space) or *lateral* (at he second or third intercostal space in the posterior idclavicular line). Single catheters were always suured in the paravertebral location (Table 1). The osition of catheter tips was radiologically confirmed the recovery room.

(b) Upon emergence, patients were taken to the ecovery room awake and extubated. At the first omplaint of pain, patients with a single catheter eceived 20 mL of 0.5% bupivacaine with 1:200,000 pinephrine through the catheter (group SE—Table). Patients with two interpleural catheters were andomized to receive 10 mL of 0.5% bupivacaine ith or without 1:200,000 epinephrine through each f two catheters (groups DE and DP—Table 1). Injecons were performed over 2–3 min in the supine osition. Patients remained in the supine position for 0 min after injection. Thoracostomy tubes were not lamped.

Subsequent doses of 20 mL of bupivacaine were iven every 4 h upon demand to a maximum of six jections over 24 h. If analgesia was inadequate, atients could receive 0.06 mg/kg morphine intraveously in the recovery room or 0.1 mg/kg intramusularly every 4 h on the ward upon request.

Five milliliter aliquots of blood were withdrawn via dial artery catheters before initial injection of local nesthetic and at 1, 3, 5, 10, 15, 20, 25, 30, 45, 60, 120, 80, and 240 min after injection. Samples were stored t −20°C in glass tubes containing sodium heparin ntil the time of analysis.

Five milliliter aliquots of pleural fluid were colcted from thoroughly mixed thoracostomy tube rainage at 240 min after local anesthetic injection. otal volume of thoracostomy tube drainage was corded at time of sampling to calculate loss of upivacaine via this route.

Bupivacaine concentrations in both whole blood and pleural drainage were determined by gas chromatography (5) and reported as micrograms bupivacaine HCl per milliliter fluid. The coefficient of variation of the assay was 10% at 0.10 μg/mL and 5% at 1.00 μg/mL. Mean peak bupivacaine concentration (C_{max}), mean time to peak concentration (T_{max}), mean content of bupivacaine (mg) in thoracostomy drainage after 4 h, and mean drainage volume (mL) after 4 h were calculated for all study groups.

Verbal numerical pain scores (VNS) (6), the presence of paravertebral and/or intercostal pinprick anesthesia, and cephalad level of pinprick anesthesia were determined at 30, 60, 90, and 240 min after the first injection of bupivacaine. A mean pain score for each patient was calculated from the four individual scores, and group means were determined.

Patients' demands for opioid were used to estimate degree of analgesia after the initial 4 postoperative hours. Total opioid usage was cumulated for each patient intraoperatively and at 8 and 24 h after the initial interpleural injection. All dosages were converted to equianalgesic morphine equivalents (mg) (7), and group means were determined.

Differences among groups were analyzed using analysis of variance and the two-tailed unpaired *t*-test. Least-squares linear regression analysis was used to determine correlation between "effective" bupivacaine dose (initial bupivacaine dose minus measured thoracostomy drainage bupivacaine) and C_{max}. Spearman ρ was used to determine correlations among C_{max}, T_{max}, thoracostomy drainage bupivacaine content (mg), and pain score. Similar analyses were performed for opioid use.

Results

There were no significant differences among the study groups with respect to age, weight, or gender.

Evaluation of Analgesia

There were no significant differences among the three study groups with respect to the analgesic effect of the first (assessed by pain score) and second (assessed by opioid use at 8 h) bupivacaine injections (Table 2). During subsequent hours (ninth through 24th), however, the single-catheter group (SE) required significantly more opioid than the double-catheter groups (DE and DP) ($P < 0.02$), despite a similar number of bupivacaine injections (Table 2). There was no difference in adequacy of analgesia

Table 2. Comparison of Analgesia Among Catheter Groups

	Group DE	Group DP	Group SE	Statistical significance
No. interpleural injections over 24 h	4.7 ± 0.4	4.8 ± 0.2	4.9 ± 0.4	NS
Pain score, 4 h (VNS)	4.5 ± 1.1	4.1 ± 1.0	6.3 ± 0.7	NS
Morphine, intraoperative (mg)	34.1 ± 3.0	54.0 ± 8.4	28.0 ± 2.5	$P < 0.01$[a]
Morphine, 0–8 h (mg)	11.9 ± 5.0	12.2 ± 5.3	18.0 ± 2.5	NS
Morphine, 9–24 h (mg)	21.9 ± 7.2	15.0 ± 4.7	42.7 ± 5.4	$P < 0.02$[b]
Total postoperative morphine, 0–24 h (mg)	33.8 ± 12.0	27.2 ± 6.3	60.7 ± 7.1	$P < 0.05$[c]

VNS, verbal numerical pain score; NS, not statistically different.
Values are expressed as mean ± SEM.
[a] Group DP is significantly different from groups DE and SE.
[b] Group SE is significantly different from groups DE and DP.
[c] Group SE is significantly different from groups DE and DP.

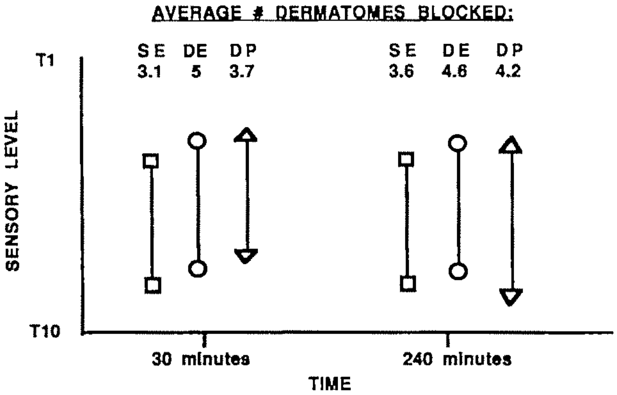


Figure 1. Dermatomal distribution (range and average number of dermatomes blocked) of pinprick anesthesia as measured in the anterior midclavicular line at 30 min and 240 min after the initial bupivacaine dose.

between groups DE and DP at any time interval during the 24-h postoperative observation period as evaluated by VNS or opioid usage. A graphic representation of the extent of sensory anesthesia is shown in Figure 1. Of note was the consistent complaint of paravertebral pain on the side of the incision in all study groups (associated with absence of pinprick anesthesia over the same area).

Bupivacaine in Thoracostomy Drainage

There were no differences among the study groups in loss of bupivacaine over 4 h (Table 3). Approximately 30–40 mg of bupivacaine was lost via this route after initial interpleural injection.

Mean peak concentration of bupivacaine in blood was numerically greater in the group receiving bupivacaine without epinephrine, but there was no statistical difference observed among the study groups with respect to C_{max} (Table 3). The maximum concentration observed in group DP was 2.47 μg/mL as compared to 0.96 μg/mL and 0.42 μg/mL in groups SE and DE, respectively.

When the initial dose of bupivacaine (100 mg) was corrected for amount lost by thoracostomy drainage at 4 h, there was no significant correlation between the effective dose administered and C_{max}. Thus, for increasing amounts of bupivacaine apparently administered to pleura, there were no concomitant increases in blood concentrations of bupivacaine.

Correlational Analysis

Neither pain scores nor opioid requirements were influenced by T_{max}, C_{max}, sensory level, bupivacaine content of thoracostomy drainage, or thoracostomy drainage volume. Use of two catheters was associated with significantly less opioid demand after the initial 8-h period ($P < 0.03$).

Discussion

The efficacy of interpleural analgesia in postthoracotomy patients appears to be enhanced by use of a double-catheter technique. Addition of epinephrine to bupivacaine did not influence degree of analgesia.

Opioid demand was used to assess adequacy of interpleural analgesia. From the ninth through 24th postoperative hours, groups DE and DP received significantly less opioid than patients with single catheters (Table 2). Administration of large amounts of intraoperative opioids in group DP may have confounded appreciation of differences in analgesic efficacy among catheter groups over the first 8 postoperative hours. Due to known pharmacokinetics and pharmacodynamics of the opioids employed (fentanyl and morphine), their analgesic effect would be negligible by the eighth postoperative hour (8).

Table 3. Comparison of Thoracostomy Drainage Volume and Bupivacaine Content, Effective (True) Bupivacaine Dose, C_{max}, and T_{max} Among Catheter Groups

	Group DE	Group DP	Group SE	Statistical significance
Thoracostomy drainage volume, 4 h (mL)	172.5 ± 20.3	197.3 ± 42.4	140.0 ± 33.6	NS
Thoracostomy drainage bupivacaine dose, 4 h (mg)	40.1 ± 13.9	30.1 ± 10.8	35.0 ± 11.4	NS
Initial effective bupivacaine dose (mg)[a]	59.9 ± 13.9	69.9 ± 10.8	65.0 ± 11.4	NS
C_{max} (μg/mL)	0.21 ± 0.07	0.79 ± 0.25	0.29 ± 0.12	NS
T_{max} (min)	4.7 ± 2.7	5.8 ± 1.8	3.4 ± 4.1	NS

C_{max}, peak bupivacaine concentration in blood; T_{max}, time to peak concentration; NS, not statistically different.
Values are expressed as mean ± SEM.
[a] Effective bupivacaine dose = 100 mg − thoracostomy drainage bupivacaine (mg).

It has been speculated that lack of adequate analgesia in postthoracotomy patients receiving interpleural analgesia may be related to loss of local anesthetic via the thoracostomy tube (1). Previous studies measured only concentration of bupivacaine, not the actual amount of drug in thoracostomy drainage (1). Because both bupivacaine concentration and drainage volume were measured in the present study, an "effective" or true initial dose could be calculated (100 mg bupivacaine minus thoracostomy drainage). An average of 30–40 mg of bupivacaine was lost over a 4-h period via the thoracostomy tube. This may account for reported decreased efficacy of interpleural analgesia in postthoracotomy patients (1,2) compared to other surgical patients in whom no thoracostomy tube was present (e.g., postcholecystectomy patients) (9).

The difference in analgesic efficacy between single- and double-catheter groups may be related to spatial distribution of local anesthetic within the interpleural space. Injection of 18 mL of 0.5% bupivacaine and 2 mL of contrast material has been shown to fill the interpleural space within 30 s in patients undergoing nonpulmonary procedures (9). The same may not be true of patients undergoing thoracotomy with removal of lung parenchyma. A degree of spread of local anesthetic over the pleural surface is probably necessary to achieve adequate analgesia. Use of two catheters may allow greater distribution of local anesthetic after thoracotomy. In the present study, patients with two catheters had better analgesia over 24 h as assessed by opioid demand. However, because of the design of this study, we cannot determine whether a single lateral catheter, or single or double catheters with multiple exit ports to enhance spread of local anesthetic, would have been as effective as the two catheters employed.

No prior study has attempted to control for catheter tip location as a factor important in determining quality of analgesia. A properly positioned interpleural catheter lies between the visceral and parietal pleura (Figure 2). The mechanism of interpleural analgesia is believed to be related primarily to local anesthetic diffusion through parietal pleura and intercostalis intimus muscle to reach intercostal nerves (10). The intercostalis intimus muscle is poorly developed or essentially absent in the upper intercostal spaces. Upper intercostal spaces may therefore be optimal for catheter tip location because one structural barrier to diffusion of local anesthetic is essentially absent. The catheter tip may be placed posteriorly to maximize paravertebral neural blockade (arrow A, Figure 3) or laterally to maximize the probability of intercostal neural blockade (arrow B, Figure 3).

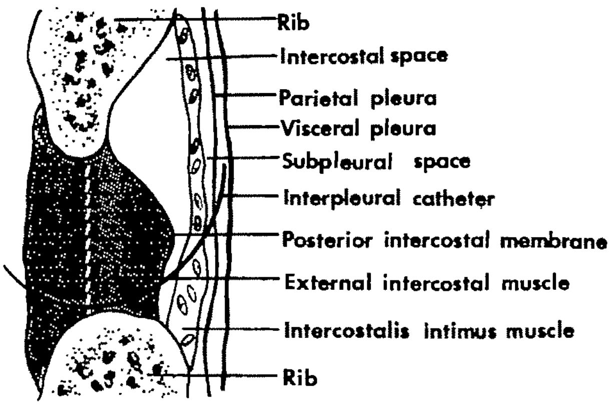


Figure 2. Cross section of the intercostal space showing an interpleural catheter lying between visceral and parietal pleura.

Because the dorsal root ganglion lies proximal to the anterior and posterior spinal nerve rami, local anesthetic reaching it from the paravertebral space (shaded triangle, Figure 3) should cause analgesia and anesthesia in the distributions of both rami. Patients in this study consistently complained of paravertebral pain (associated with absence of pinprick anesthesia) on the thoracotomy side. A major component of postthoracotomy pain results from

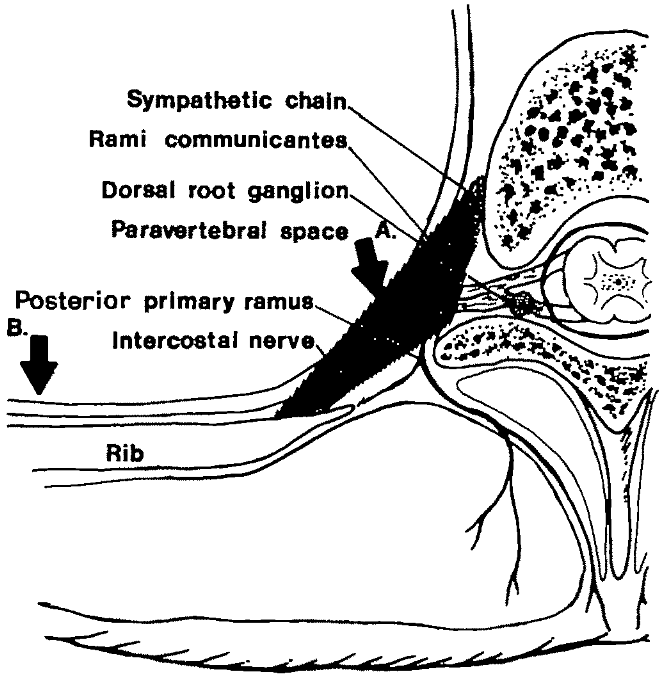


Figure 3. Transverse section at level of intervertebral foramen. *Shaded triangle* represents paravertebral space. *Arrow A* represents most optimal catheter location for blockade of paravertebral neural structures. More lateral placement of a catheter (*arrow B*) would produce intercostal nerve block.

injury to muscular and ligamentous structures in this area. The structures are innervated by posterior rami of the appropriate spinal nerves (11). The results of this study suggest that interpleural analgesia does not achieve paravertebral neural blockade in supine thoracotomy patients.

When the patient is in the supine position, blood and extravasated tissue fluid preferentially flow by gravity toward the paravertebral gutter. Placement of the catheter tip close to the paravertebral gutter (arrow A, Figure 3) may promote mixture and dilution of local anesthetic with blood and extravasated fluid, which may decrease efficacy. In an animal model, neural blockade has been found to localize over dependent structures, indicating a strong influence of gravity (10). The results of this study are referable to the supine position and may not be the same in other body positions. The segmental anesthesia obtained with a single paravertebral catheter probably was due to lateral spread of local anesthetic to block intercostal nerves.

Our conclusions are as follows: (a) epinephrine does not improve the degree of interpleural analgesia after thoracotomy; (b) actual loss of bupivacaine via thoracostomy tube drainage after 4 h is substantial (30%–40% of administered dose); (c) for supine post-thoracotomy patients, analgesia is related to blockade of nerves in the intercostal rather than paravertebral space; and (d) use of a double-catheter technique enhanced the efficacy of interpleural analgesia in postthoracotomy patients.

References

1. Rosenberg PH, Scheinin BMA, Lepäntolo MJA, Lindfors O. Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 1987;67:811–3.
2. El-Baz N, Faber LP. Intrapleural infusion of local anesthetic: a word of caution (letter). Anesthesiology 1988;68:809–10.
3. Kambam JR, Hammon J, Parris WCV, Lupinetti FM. Intrapleural analgesia for postthoracotomy pain and blood levels of bupivacaine following intrapleural injection. Can J Anaesth 1989;36:106–9.
4. Symreng T, Gomez MN, Johnson B, Rossi NP. Intrapleural bupivacaine vs saline after thoracotomy—effects on pain and lung function—a double blind study (abstract). Anesth Analg 1988;67:S227.
5. Tucker GT. Determination of bupivacaine (marcaine) and other anilide-type local anesthetics in human blood and plasma by gas chromatography. Anesthesiology 1970;32:255–60.
6. Murphy DF, McDonald A, Power C, Unwin A, MacSullivan R. Measurement of pain: a comparison of the visual analogue with a nonvisual analogue scale. Clin J Pain 1987;3:197–9.
7. Foley KM. The treatment of cancer pain. N Engl J Med 1985;313:84–95.
8. Stoelting RK. Pharmacology and physiology in anesthetic practice. Philadelphia: J. B. Lippincott, 1987:73–86.
9. Reiestad F, Stromskag KE. Interpleural catheter in the management of postoperative pain. A preliminary report. Reg Anesth 1986;11:89–91.
10. Riegler FX, VadeBoncouer TR, Pelligrino DA. Interpleural anesthetics in the dog: differential somatic neural blockade. Anesthesiology 1989;71:744–50.
11. Eason MJ, Wyatt R. Paravertebral thoracic block—a reappraisal. Anaesthesia 1979;34:638–42.

Comparison of Vecuronium- and Atracurium-Induced Neuromuscular Blockade in Postpartum and Nonpregnant Patients

Karin S. Khuenl-Brady, MD, Johann Koller, MD, Peter Mair, MD, Friedrich Pühringer, MD, and Gottfried Mitterschiffthaler, MD

KHUENL-BRADY KS, KOLLER J, MAIR P, PÜHRINGER F, MITTERSCHIFFTHALER G. Comparison of vecuronium- and atracurium-induced neuromuscular blockade in postpartum and nonpregnant patients. Anesth Analg 1991;72:110–3.

The time-course of action of 0.1 mg/kg vecuronium and 0.5 mg/kg atracurium was investigated in nonpregnant and in postpartum patients within 4 days after delivery. The clinical duration of vecuronium, but not that of atracurium, was significantly prolonged in the latter group ($P < 0.001$) and averaged 36 ± 6 and 37 ± 4 min for atracurium and 32 ± 6 and 49 ± 10 min for vecuronium in nonpregnant and in postpartum patients, respectively (mean ± SD). In additional in vitro experiments in the rat phrenic nerve-hemidiaphragm preparation no difference could be observed in the neuromuscular blocking effects of vecuronium in postpartum and nonpregnant female rats. It is concluded that pregnancy-induced changes in liver blood flow and/or competition for the liver uptake of sexual hormones might interfere with the hepatic clearance of vecuronium in postpartum patients and thereby cause the observed prolongation of neuromuscular blockade.

Key Words: NEUROMUSCULAR RELAXANTS, VECURONIUM, ATRACURIUM. ANESTHESIA, OBSTETRICS.

Hemodynamic and hormonal changes associated with pregnancy may modify the pharmacologic and/or pharmacokinetic profile of some drugs (1), including neuromuscular blocking agents. Dailey et al. (2), for example, in their study of pharmacokinetics of pancuronium and vecuronium in patients undergoing cesarean section, found the elimination half-lives of both drugs to be shorter and the total body clearance higher, without, however, significant differences in their time-course of action, when compared with nonpregnant patients. In pregnant rabbits Rodrigue et al. (3) observed a shift to the left of the dose-response curve of vecuronium, indicating an increase in potency. Indeed, in the postpartum period the reestablishment of normal blood pressure and body weight as well as the ongoing changes in hormone levels and lactation have been reported to prolong appreciably the duration of action of vecuronium in patients within 4 days after delivery (4,5).

Vecuronium is a high hepatic excretion compound (6,7). One might, therefore, speculate that the above-observed prolongation of its neuromuscular blocking effects might be due to pregnancy-induced changes in liver function or liver blood flow. Atracurium could serve as a useful tool to test this possibility because its neuromuscular effects are terminated by chemical degradation independent of the excretory organ functions or enzyme systems (8).

This study was undertaken to compare the neuromuscular blocking effects of vecuronium and atracurium in postpartum patients. In an attempt to differentiate between the contributions of pharmacokinetic and pharmacodynamic factors to the effects of pregnancy on the neuromuscular blocking effects of vecuronium, studies in patients were supplemented by additional in vitro studies using the rat hemidiaphragm preparations from postpartum and nonpregnant female rats.

Methods

Clinical Study

After institutional approval 60 consenting ASA physical status I or II female patients were included in this study. Thirty of them were within 4 days of delivery

---

Received from the Clinics for Anaesthesia and General Intensive Care Medicine, University of Innsbruck, Austria. Accepted for publication September 5, 1990.

Address correspondence to Dr. Khuenl-Brady, Clinics for Anaesthesia and General Intensive Care Medicine, University of Innsbruck, Anichstrasse 35, A - 6020 Innsbruck, Austria.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

and scheduled to undergo sterilization via laparoscopic tubal cauterization. The remaining patients underwent elective gynecologic procedures of the same duration (approximately 30–50 min). All patients were free of neuromuscular diseases and did not receive any medication known to alter neuromuscular transmission.

Anesthesia was induced in nonpremedicated patients with 4–5 mg/kg thiopental or 1.5–2 mg/kg methohexital and 0.003 mg/kg fentanyl. Once the patient was asleep, assessment of neuromuscular function was started. Supramaximal train-of-four stimuli of 2 Hz were delivered every 20 s to the right ulnar nerve at the wrist through surface electrodes, and the evoked electromyogram responses of the hypothenar muscles were recorded via a Datex monitor. Once the recorded electromyogram was stabilized, either 0.1 mg/kg vecuronium bromide or 0.5 mg/kg atracurium besylate was injected into a rapidly running intravenous infusion. Tracheal intubation was performed after maximum blocking effect was established. Anesthesia was maintained with nitrous oxide in oxygen (2:1) and additional doses of fentanyl if required.

When the train-of-four ratio became greater than zero (first appearance of the fourth twitch) the residual neuromuscular block was antagonized with 30 μg/kg neostigmine administered together with 10 μg/kg atropine. Time-course parameters including the onset of block (time from injection until 95% twitch depression) and clinical duration of action (time from injection until the first appearance of the fourth twitch in the train-of-four) of both drugs were recorded and compared in the two groups.

Animal Study

After approval by the local committee on animal research, female Wistar rats, weighing between 180 and 300 g, were anesthetized with 10 mg/kg thiopental intraperitoneally and decapitated. The left hemidiaphragms (n = 12) were dissected with their accompanying phrenic nerve. The preparations were placed in an organ bath containing a modified Krebs–Ringer solution aerated with carbogen (5% carbon dioxide in 95% oxygen) and maintained at 36.5–37°C. The pH was measured at regular intervals during the experiments and was found to remain constant at 7.32–7.42. The tendon of the hemidiaphragm was connected to a Grass FT-03 transducer, and a preload of 5–10 g was applied. The phrenic nerve was stimulated via a Grass SS88 stimulator using supramaximal square wave stimuli of 0.2 ms duration at a frequency of 0.1 Hz. The resultant force of the muscle contractions was recorded on a Graphtec printer. Each preparation was allowed to stabilize for at least 20 min until a stable twitch height was achieved.

Table 1. Patients' Characteristics

	Atracurium (n = 30)		Vecuronium (n = 30)	
	Postpartum	Nonpregnant	Postpartum	Nonpregnant
Age (yr)	32 ± 8	31 ± 4	31 ± 10	33 ± 5
Weight (kg)	59 ± 10	64 ± 9	61 ± 10	66 ± 9
Height (cm)	164 ± 6	165 ± 4	166 ± 3	163 ± 4
BSA (m^2)	1.6 ± 0.2	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1

BSA, body surface area.
All values are expressed as mean ± SD.

Cumulative doses of 0.5 μmol vecuronium were added to the bath, and dose-response relationships were investigated in the diaphragms of both nonpregnant female rats (n = 5) and rats within 2–12 h after delivery (n = 7).

For the statistical analysis of the data, Student's t-test for unpaired data was used and differences considered as significant at $P < 0.05$.

Results

Demographic data, as shown in Table 1, did not differ significantly in postpartum and nonpregnant patients. Onset time was 2 ± 0.7 and 3 ± 1 min for atracurium and 2 ± 0.7 and 3 ± 1 min for vecuronium in normal and postpartum patients, respectively (Figure 1). In contrast to the duration of atracurium, 37 ± 4 versus 36 ± 6 min, the clinical duration of action of vecuronium, 49 ± 10 versus 32 ± 6 min, was significantly longer ($P < 0.001$) in postpartum than in control patients.

The dose-response relationship of vecuronium observed in the two in vitro experimental groups is shown in Figure 2. The ED_{25}, ED_{50}, and ED_{75} values derived from the dose-response curves did not differ significantly in the two groups and were 2.8, 3.7, 4.7 μmol/L and 3.3, 4.3, 5.1 μmol/L in diaphragms of postpartum and nonpregnant rats, respectively.

Discussion

Physiologic homeostatic changes during and shortly after pregnancy include shift in fluids associated with gain in weight, increased hormone levels, and reestablishment of normal blood pressure. A decrease in the elimination half-life and an increase in total body

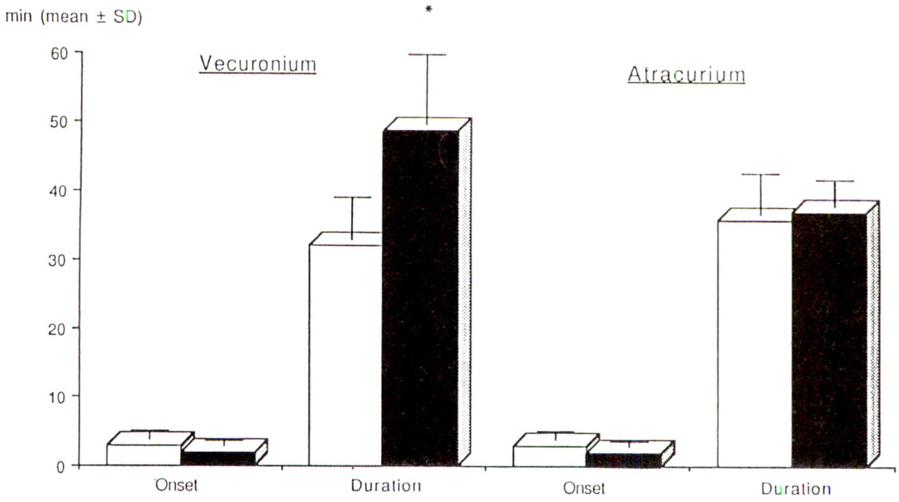


Figure 1. Time-course of action of vecuronium (0.1 mg/kg) and atracurium (0.5 mg/kg) in postpartum (*solid bar*) and nonpregnant (control, *open bar*) patients. $^*P < 0.001$.

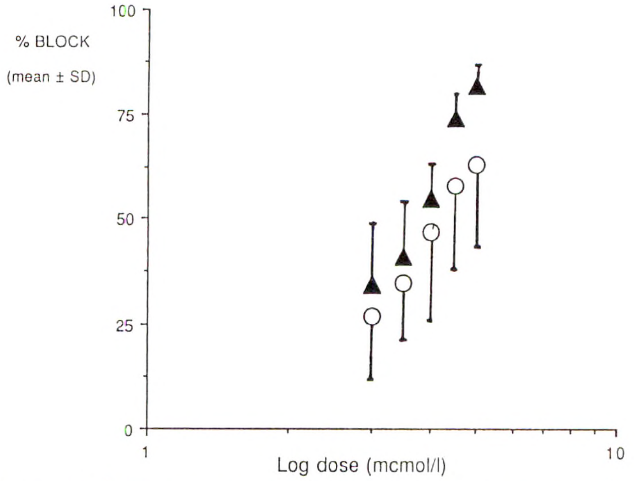


Figure 2. Dose-response relationship of vecuronium in diaphragms of postpartum (○, n = 7) and nonpregnant (control, ▲, n = 5) rats.

clearance has been reported after pancuronium in patients undergoing cesarean section when compared with nonpregnant controls (2). These changes were related to the acute blood loss during surgery or facilitated renal and hepatic elimination due to pregnancy. In contrast to the above observations (2), the only significant change in our study is the prolonged duration of action of vecuronium in postpartum patients. This confirms the observations reported in similar studies by others (4,5). The time-course of action of the neuromuscular blocking effects of atracurium appeared to be not affected by the postpartal state of the patients. We assumed that if the changes observed with vecuronium had been caused by the alterations in blood volume or the volume of distribution only, they would have probably affected (at least to a limited extent) atracurium in a similar way. The results of our study do not support this assumption (4,5); therefore, other factors should be considered as possible reasons for the prolonged duration of action of vecuronium in the postpartum period.

Body weight as well as total body fat may increase during pregnancy. Postpartum patients usually weigh more than in the nonpregnant state. Vecuronium has a prolonged duration of action in overweight or obese nonpregnant patients (9), possibly because of occult abnormal liver function in obesity. Because atracurium is less dependent on organ function for its elimination, its duration of action is not expected to be prolonged in overweight patients. In the present study the two groups of vecuronium-treated patients had similar weight and body surface area (Table 1). Although we did not determine total body fat content or lean body mass, there is little reason to believe that obesity associated with occult liver histopathology played an important role in our findings. However, the appreciation of relative overweight inherent to the postpartal state of the patients by adjustment of the dose of vecuronium to ideal body weight might have prevented its prolonged duration of action in the present study.

During pregnancy total plasma volume increases by 30%–40% but liver blood flow is maintained at nonpregnant levels. Thus a net decrease in liver blood flow (approximately 20%) exists during pregnancy (10). Because vecuronium is a high hepatic clearance drug, its elimination might be profoundly affected by liver blood flow (11). A relative decrease in hepatic flow might have been partly responsible for its decreased rate of elimination in postpartum patients. Increased steroidal hormone levels might, however, also affect the muscle itself in a similar fashion as corticosteroids (12). The results of our in vitro study, nevertheless, show that pregnancy-induced changes do not seem to affect neuromuscular transmission or muscle contractility. The response to vecuronium was the same in diaphragms of nonpregnant and postpartum rats. The extent to which the present in vitro results reflect changes in human muscle in the postpartum period remains to be elucidated.

Vecuronium is rapidly taken up by the liver, as are steroidal sexual hormones that are metabolized in the liver (10). Competition of vecuronium and these hormones at various binding sites on their way through the liver may occur. Transport mechanisms in the liver might become saturated by the elevated hormone levels in the pregnant and postpartum state. Albumin levels are decreased during pregnancy (13). Although the extent of protein binding of vecuronium is still a controversial issue (14), hypoproteinemic states would prolong its duration of neuromuscular blocking effects in the case of appreciable protein binding.

In summary, we have shown that the duration of action of vecuronium is prolonged in postpartum patients, whereas that of atracurium is not. Because the in vitro part of this study did not prove any difference in the response of postpartum and nonpregnant rat diaphragms to vecuronium, the most probable explanation for the above findings in humans is changes in hepatic blood flow associated with pregnancy and the postpartum period, or hormonally induced reduction of the liver uptake of vecuronium. The extent to which a relative overdose due to "relative overweight" inherent to pregnant and postpartum patients contributes to the prolonged duration of action of vecuronium remains to be elucidated.

References

1. Dam M, Christiansen J, Munck O, Mygind KI. Antiepileptic drugs: metabolism in pregnancy. Clin Pharmacokinet 1979;4:53–62.
2. Dailey PA, Fisher DM, Shnider SM, et al. Pharmacokinetics, placental transfer and neonatal effects of vecuronium and pancuronium administered during cesarean section. Anesthesiology 1984;60:569–74.
3. Rodrigue R, Durant NN, Nguyen N, Latz L, Conklin KA. Comparison of vecuronium induced neuromuscular blockade in pregnant and non-pregnant female rabbits. Anesthesiology 1986;65:A401.
4. Camp CE, Tessem J, Adenwala J, Joyce TH. Vecuronium and prolonged neuromuscular blockade in postpartum patients. Anesthesiology 1987;67:1006–8.
5. Hawkins JL, Adenwala J, Camp CE, Joyce TH. The effect of H_2-receptor antagonist premedication on the duration of vecuronium-induced neuromuscular blockade in postpartum patients. Anesthesiology 1989;71:175–7
6. Bencini AF, Mol WEM, Scaf AHJ, Kersten UW, Wolters KTP, Agoston S. Uptake and excretion of vecuronium bromide and pancuronium bromide in the isolated perfused rat liver. Anesthesiology 1988;69:487–92.
7. Bencini AF, Scaf AHJ, Sohn YJ, Kersten-Kleef UW, Agoston S. Hepatobiliary disposition of vecuronium bromide in man. Br J Anaesth 1986;58:988–94.
8. Stenlake JB, Waigh RD, Urwin J, Dewar GH, Coker GG. Atracurium: conception and inception. Br J Anaesth 1983;55:3–10S.
9. Weinstein JA, Matteo RS, Ornstein E, Schwartz AE, Goldstoff M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. Anesth Analg 1988;67:1149–53.
10. Van Thiel DH, Gavaler JS. Pregnancy-associated sex steroids and their effects on the liver. Semin Liver Dis 1987;7:1–7.
11. Wierda JMKH, Scarf AHJ, Hennis PJ, et al. The influence of hypothermia on the pharmacokinetics of vecuronium. A clinical study in patients undergoing surface cooling or hypothermic bypass. Doctoral thesis, University of Groningen, Groningen, The Netherlands, 1990:159–71.
12. Mandel S. Steroid myopathy. Postgrad Med J 1982;72:207–15.
13. Esbjöner E, Järnerot G, Sandström B, Östling G. Serum albumin reserve for bilirubin binding during pregnancy in healthy women. Obstet Gynecol 1986;73:93–6.
14. Bencini AF. Pharmacokinetic basis of the neuromuscular blocking effects of vecuronium bromide in man. Doctoral thesis, University of Groningen, Groningen, The Netherlands, 1986:36.

ANESTH ANALG
1991;72:114–9

Effects of Hydralazine and Prostaglandin E_1 on Regional Myocardial Function in the Ischemic Canine Heart

Shigeho Morita, MD, Hisato Takahashi, MD, Masashi Kono, MD, Yukihiko Uno, MD, Midori Ozawa, MD, and Toshiro Sato, BS

MORITA S, TAKAHASHI H, KONO M, UNO Y, OZAWA M, SATO T. Effects of hydralazine and prostaglandin E_1 on regional myocardial function in the ischemic canine heart. Anesth Analg 1991;72:114–9

The effects of hydralazine and prostaglandin E_1 on regional myocardial function were studied in dogs. Sixteen dogs were randomly assigned to one of two drug treatment groups of eight dogs each. The first group (G1) was treated with 0.4 mg/kg hydralazine administered as a bolus. The second group (G2) received prostaglandin E_1 given as an infusion for a total dose of 0.8 μg/kg. Regional myocardial function was assessed through the measurement of myocardial segment shortening during systole. We call this index percent systolic shortening (%SS). An ischemic heart preparation was created by partial occlusion of coronary blood flow. The degree of induced ischemia was determined by following the reduction in %SS. Hydralazine reduced %SS of the ischemic myocardium while increasing the cardiac index, stroke volume index, and coronary blood flow. Prostaglandin E_1 increased %SS, cardiac index, and stroke volume index in the ischemic heart preparation. Hydralazine, therefore, induced dissociation between global ventricular function and regional myocardial function whereas prostaglandin E_1 did not. The present findings emphasize that evaluation of vasoactive drugs should consider their effects on regional myocardial function as well as on global hemodynamics.

Key Words: HEART, ISCHEMIA—regional. PHARMACOLOGY, HYDRALAZINE. HORMONES, PROSTAGLANDIN E_1.

Vasodilators have been extensively used to treat myocardial ischemia. Typical applications include blood pressure control and afterload reduction in the failing heart. Some vasodilators, however, may prove deleterious to ischemic hearts. Sodium nitroprusside, for example, may worsen myocardial ischemia, probably secondary to nonspecific coronary vasodilation leading to coronary steal (1).

Regional myocardial function (RMF) has been highlighted as a more sensitive indicator of myocardial ischemia than global ventricular function (GVF) (2). This is because GVF as measured by clinical monitoring of hemodynamics and the electrocardiogram may not reflect early myocardial ischemia.

In patients with ischemic heart disease, RMF may become dissociated from GVF. In other words, abnormalities of RMF may appear without changes in GVF as measured by monitoring commonly employed in the operating room (3). Efficacy of vasodilator therapy under anesthesia should therefore be assessed by an analysis of RMF as well as the more routinely evaluated GVF.

Prostaglandin E_1 (PGE_1) has gained popularity in Japan for inducing deliberate hypotension intraoperatively and as an agent for afterload reduction in the setting of perioperative hypertension. Our clinical practice is to administer hydralazine by bolus and PGE_1 by infusion. Bolus administration of PGE_1 is not done because the resulting duration of action is too short to produce a clinically useful effect. We believed it worthwhile to examine the effects of PGE_1 on ischemic myocardium and therefore constructed the following experiment.

Methods

Sixteen adult mongrel dogs of either sex, weighing 15–28 kg, were randomly assigned to one of two drug treatment groups of eight dogs each. Animals used in this study were maintained in accordance with the

---

Supported by Teikyo University.

Received from the Teikyo University School of Medicine, Department of Anesthesia, Ichihara Hospital, Ichihara City, Chiba, Japan. Accepted for publication September 6, 1990.

Address correspondence to Dr. Morita, Teikyo University School of Medicine, Department of Anesthesia, Ichihara Hospital, 3426-3, Anesaki, Ichihara City, Chiba 299-01, Japan.

©1991 by the International Anesthesia Research Society

guidelines of the Committee on Animals in Research of the Teikyo University School of Medicine. We designated the hydralazine-treated group G1 and the PGE$_1$-treated group G2.

Anesthesia was induced with pentobarbital (30 mg/kg) and maintained with 0.1%–0.5% inspired concentration of enflurane in oxygen. After femoral vein cannulation, saline was administered intravenously at a rate of 5 $\mathrm{mL \cdot kg^{-1} \cdot h^{-1}}$. The dogs were given pancuronium bromide (0.05 mg/kg) and were artificially ventilated with a Harvard Respirator (model SN-480-3 Tokyo). Periodic arterial blood gas determinations were made from samples drawn from a femoral arterial cannula and parameters maintained at P_{O_2} = 80–200 mm Hg and P_{CO_2} = 35–40 mm Hg.

Hemodynamics were measured via disposable, clinical strain gauges attached to the femoral arterial cannula and to the central venous and pulmonary arterial ports of a Swan–Ganz catheter floated via a left internal jugular vein. A peripheral electrocardiograph record was obtained via a clinical electrocardiogram monitor.

A left thoracotomy was performed in the fifth intercostal space. A high-fidelity micromanometer (model D.T.X., Spectramed Medical Inc., Oxnard, Calif.) was inserted into a left ventricular stab wound at the apex. The left circumflex coronary artery (LCX) was dissected free near its origin and a 3-mm-diameter, 20-MHz pulsed Doppler flow probe (model T 101, Transonic Systems Inc., Ithaca, N.Y.) and an adjustable screw clamp of our own design were placed on the origin of the LCX. No coronary artery branch was present between the flow probe and the screw clamp. Two pairs of 5-MHz sonomicrometry microcrystals (crystals 45295, Nihon Sanei Denki Inc., Tokyo) were implanted along the short axis of the left ventricle to measure myocardial segment length. One pair was implanted within the area supplied by the left anterior descending coronary artery and the other pair within the area perfused by the LCX (Figure 1).

When myocardial ischemia was required, the LCX flow was reduced by 50%–75% by tightening the screw clamp until RMF in the area supplied by the LCX was impaired. We used percent systolic shortening (%SS) of sonomicrometer-instrumented myocardial segments as a parameter of regional myocardial ischemia. We defined %SS as

$$[(\mathrm{EDL} - \mathrm{ESL})/\mathrm{EDL}] \times 100,$$

where EDL is the end-diastolic myocardial segment length and ESL is the end-systolic myocardial segment length.

Quantitative comparison of %SS data is only possible if the %SS measurements are made in the setting of equal left ventricular end-diastolic pressure (LVEDP). An intraventricular cannula was in place throughout our experiments. Intraventricular pressures were recorded with all %SS data and used to verify that LVEDP was in fact the same during all experiments on each individual dog.

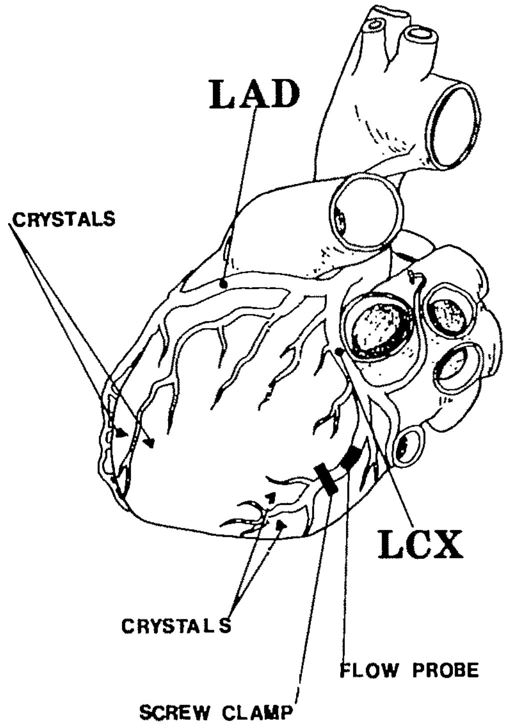


Figure 1. A schematic diagram of the canine heart preparation. Sonomicrometry microcrystals were implanted along the short axis of the left ventricle. A flow probe and the screw clamp were applied on the proximal left circumflex coronary artery. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery.

For the purposes of inducing ischemia by partial LCX screw clamp occlusion, we defined an impaired RMF as characterized by a change in %SS of 20%–30%. There was no change in LVEDP or stroke volume index after induced ischemia.

After recording prestenosis (control) data, RMF was induced by creating LCX stenosis as described. After 15 min of induced ischemia, the treatment drug was administered. G1 animals received an intravenous hydralazine bolus of 0.4 mg/kg over several seconds. G2 dogs were treated with PGE$_1$ given as an infusion at a rate of 40 $\mathrm{ng \cdot kg^{-1} \cdot min^{-1}}$ over 20 min.

All signals acquired from each dog were stored on an analog data recorder (PC-108M SONY, Tokyo). Observations were made at three times: time T_0 (control), time T_1 (after stenosis), and time T_2 (after treatment). Because the hypothesis that the data had been sampled from the population with normal distribution was not rejected statistically, the signifi-

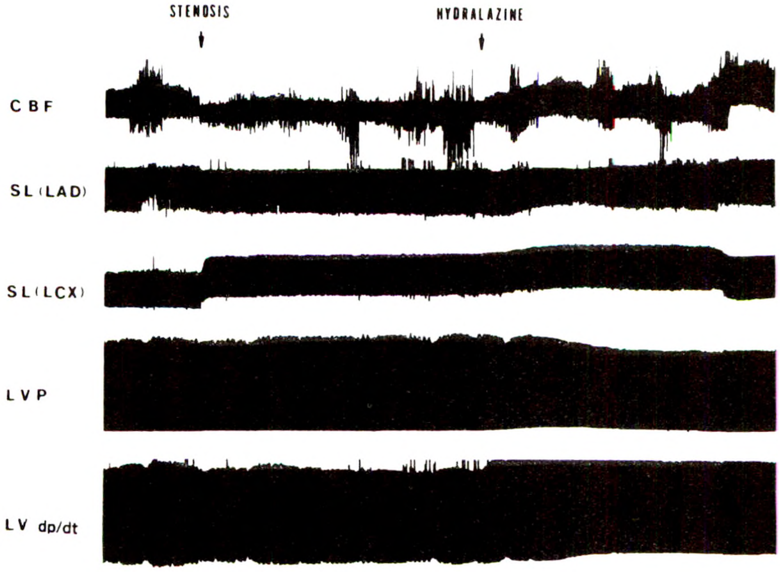


Figure 2. A representative tracing of group 1. After the LCX was stenosed, segment length of the myocardium supplied by LCX was elongated (%SS was decreased). After hydralazine administration, the segment length was elongated further. CBF, circumflex coronary blood flow; SL(LAD), segment length of the myocardium supplied by LAD; SL(LCX), segment length of the myocardium supplied by LCX; LVP, left ventricular pressure; LV dp/dt, first derivative of left ventricular pressure.

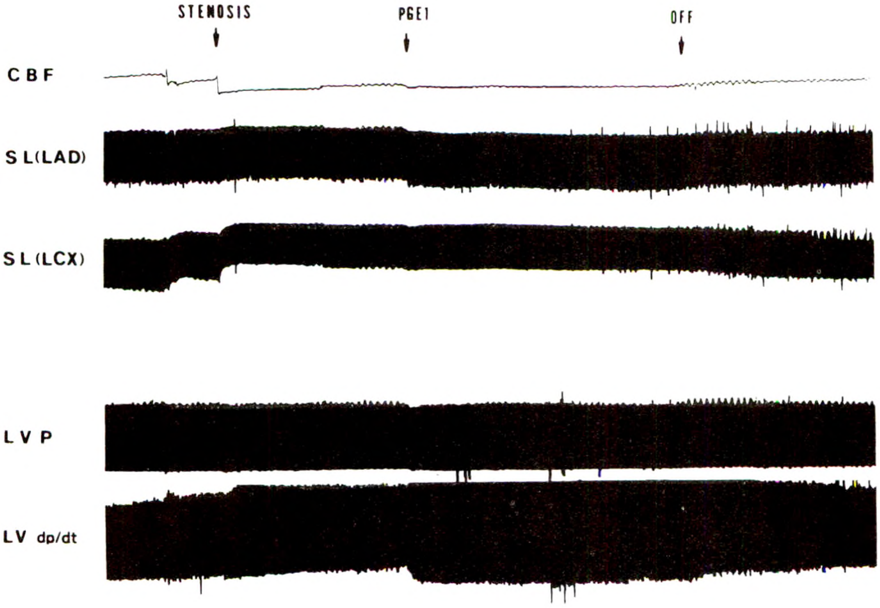


Figure 3. A representative tracing of group 2. After the LCX was stenosed, segment length of the myocardium supplied by LCX was elongated (%SS was decreased). After PGE_1 administration, the segment length was not elongated further. Abbreviations as in Figure 2.

cance of the differences between groups was determined by analysis of variance and Student-Newman-Keuls test for pairwise comparison if appropriate. A *P* value of less than 0.05 was considered to be significant.

Results

The decrease in LCX flow produced by partial LCX occlusion significantly decreased %SS of the LCX-supplied myocardium of both groups ($P < 0.01$). Global ventricular function was essentially unchanged after screw-clamp induced ischemia in G1 and G2. Administration of hydralazine significantly worsened RMF as indicated by a decreased %SS in G1. In contrast, treatment with PGE_1 improved RMF as demonstrated by the increased %SS for G2. Both G1 and G2 exhibited a striking increase in stroke volume index after treatment despite the marked difference in RMF between the groups.

G1 and G2 exhibited a significant decrease in mean arterial pressure with treatment. The hydralazine-treated group showed no change in dp/dt after treatment, whereas an increase in dp/dt was seen in the PGE_1-treated animals.

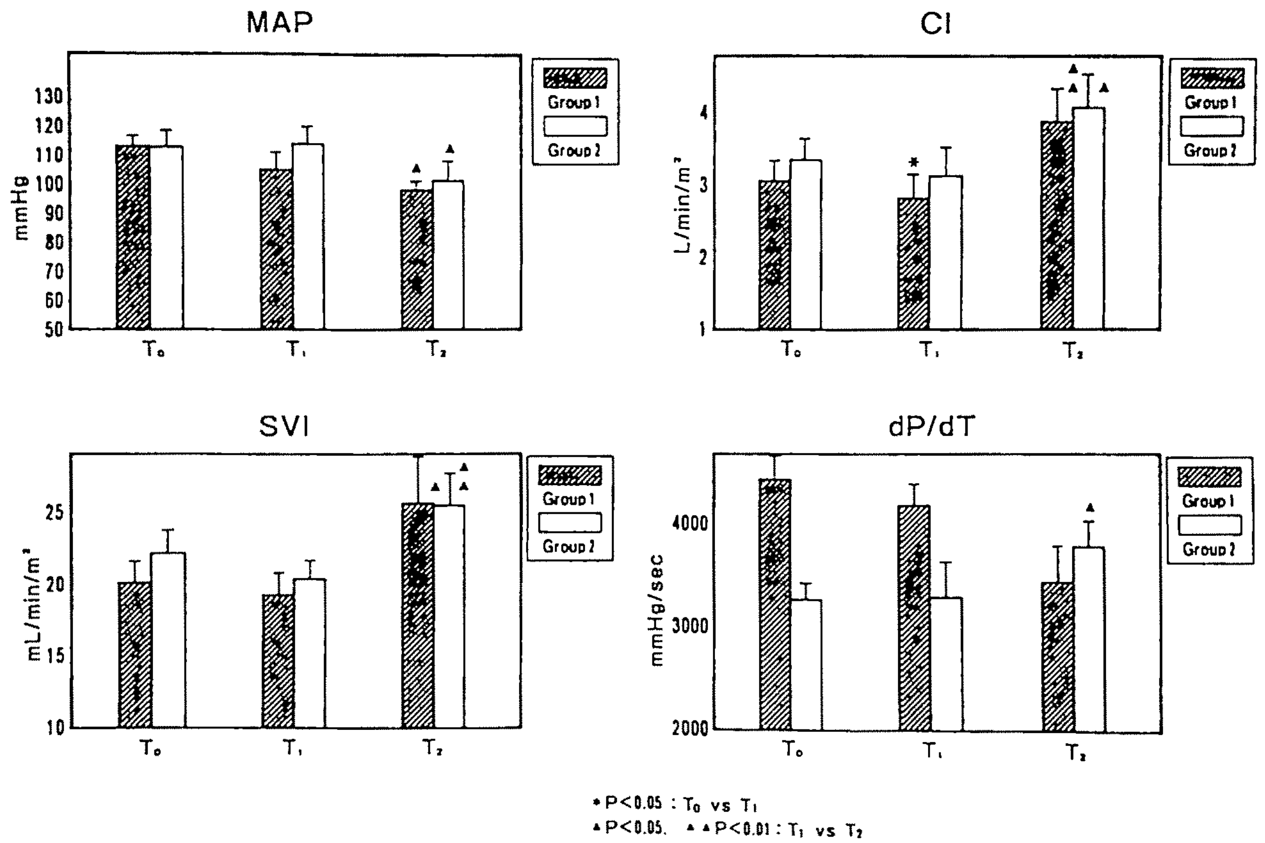


Figure 4. Hemodynamic changes before and after the treatments in groups 1 and 2. Mean arterial pressure (MAP) was decreased, and cardiac index (CI) and stroke volume index (SVI) were increased after hydralazine and PGE$_1$ administration.

Coronary artery blood flow into the ischemic preparation increased after administration of hydralazine and remained unchanged for the PGE$_1$-treated group.

Representative recordings of hemodynamics surrounding treatment in both groups are shown in Figures 2 and 3. The results are depicted in graphic form in Figures 4 and 5.

Discussion

The prestenotic values for %SS are not the same in the two groups. It is possible that the microcrystal planes were not orthogonal to each other, thus explaining this difference. However, changes in %SS with screw-clamp occlusion occurred in the same range of coronary arterial blood flow for both groups, suggesting that %SS provides an accurate way to follow ischemia in our preparation.

Unlike PGE$_1$, administration of hydralazine worsened RMF as measured by %SS. Stroke volume index proved insensitive to worsening myocardial ischemia after hydralazine administration.

Increased coronary blood flow seen after the administration of hydralazine could be partly due to hydralazine-induced increases in heart rate. This is not relevant to our experiments, however, because heart rate was stable after hydralazine administration. We believe that the worsening myocardial ischemia after hydralazine administration to our animals is caused by a coronary artery steal phenomenon similar to that seen with nitroprusside.

Prostaglandin E$_1$ appeared to have a salutary effect on RMF in our ischemic heart preparation. We believe that this could be explained by one of two mechanisms: (a) afterload reduction or (b) increased coronary blood flow. Afterload reduction would increase %SS as long as regional myocardial contractility remained at approximately the same level. In the absence of a steal phenomenon as hypothesized for hydralazine, regional myocardial blood flow would be increased with the increased total coronary artery blood flow. We saw constant coronary blood flow after PGE$_1$ administration, therefore the afterload reduction mechanism is the likely explanation.

It is generally considered that regional myocardial

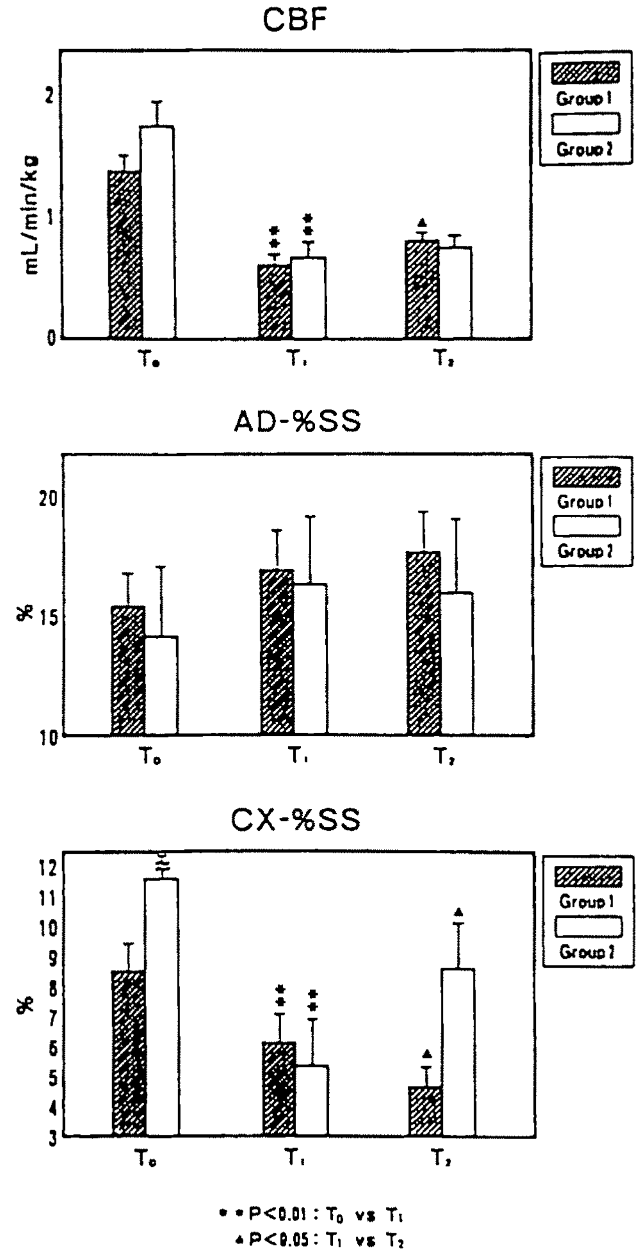


Figure 5. Regional myocardial changes before and after the treatments in groups 1 and 2. After having stenosed coronary artery, CBF and %SS were decreased significantly. After hydralazine administration, %SS was decreased in group 1 whereas it was increased in group 2.

blood flow is maintained as long as blood flow to the corresponding region is unchanged (4). However, catecholamines such as dobutamine may enhance regional myocardial systolic function despite a further decrease in subendocardial blood flow (5). Therefore, RMF and regional myocardial blood flow may dissociate with inotropic stimulation. In this study, we did not measure regional myocardial blood flow. It was therefore not clear if the above dissociation occurred with vasodilator administration in our experiment.

Percent systolic shortening (6), percent postsystolic shortening (7), and percent regional myocardial wall thickening (8) have been used as parameters of RMF. Some authors advocate regional pressure length relations (9) or end-systolic dimension-wall thickness relations (10) as load-independent parameters of RMF. It has been suggested that diastolic myocardial function is associated with early myocardial ischemia (11). Diastolic pressure-length relations or diastolic pressure-thickness relations may therefore be sensitive measures of RMF. In fact, it is generally considered that diastolic myocardial function deteriorates earlier than systolic myocardial function (12,13). However, systolic and diastolic dysfunction may have a common basis at the cellular level (14).

We have used %SS as an index of RMF because %SS consistently changed in the same direction as coronary blood flow in our experimental model. Availability of continuous ventricular pressure data allowed us to ensure that LVEDP was equal during all %SS measurements made for each individual animal.

Our experiment implies that it is clinically important to evaluate vasoactive drugs in terms of their effects on RMF as well as GVF. Therapeutic efforts focusing on the detection of myocardial ischemia by GVF may not prevent or reverse perioperative myocardial ischemia in clinical practice.

Stroke volume index may not be as sensitive an instrument for the detection of ischemia manifesting as a decrease in RMF.

Regional myocardial dysfunction represented by wall motion abnormalities diagnosed by echocardiography (15) or regional myocardial hypoperfusion detected by contrast echocardiography (16,17) may well be taken into consideration in the evaluation of therapeutic maneuvers in our daily practice of anesthesia.

References

1. Cohn JN, Franciosa JA. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure. N Engl J Med 1982;306: 1129–35.
2. Glower DD, Spratt JA, Kabas JS, et al. Quantification of regional myocardial dysfunction after acute ischemic injury. Am J Physiol 1988;255:H85–93.
3. Buda AJ, Dubbin JD, Heindok H. Radionuclide assessment of regional left ventricular function in acute myocardial infarction. Am Heart J 1986;111:36–41.
4. Smalling RW, Kelley K, Kirkeeide RL, et al. Regional myocardial function is not affected by severe coronary depressuriza-

tion provided coronary blood flow is maintained. J Am Coll Cardiol 1985;5:948–55.

5. Schulz R, Miyazaki S, Miller M, et al. Consequences of regional inotropic stimulation of ischemic myocardium on regional myocardial blood flow and function in anesthetized swine. Circ Res 1989;64:1116–26.
6. Grover GJ, Kostis JB, Weiss HR, et al. Effect of beta-adrenoceptor stimulation or blockade on regional myocardial function and regional O_2 consumption during myocardial ischemia. Arch Int Pharmacodyn Ther 1988;291:68–87.
7. Philbin DM, Foex P, Drummond G, et al. Post-systolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. Anesthesiology 1985;62:166–74.
8. Kittleson MD, Knolen GG, Johnson LE. Relationships of regional wall motion, wall thickening, and global performance. Am Heart J 1987;114:70–8.
9. Aversano T, Maughan WL, Hunter WC, et al. End-systolic measures of regional ventricular performance. Circulation 1986;73:938–50.
10. Osakad G, Hess OM, Gallagher KP, et al. End-systolic dimension-wall thickness relations during myocardial ischemia in conscious dogs. A new approach for defining regional function. Am J Cardiol 1983;51:1750–8.
11. Doyle RL, Foex P, Phil D, et al. Effects of halothane on left ventricular relaxation and early diastolic coronary blood flow in the dog. Anesthesiology 1989;70:660–6.
12. Grossman W. Diastolic dysfunction and congestive heart failure. Circulation 1990;81(Suppl 3):1–7.
13. Nest RW, Kowalchu GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987;57:23–30.
14. Glower DD, Schaper J, Kabas SJ, et al. Relation between reversal of diastolic creep and recovery of systolic function after ischemic myocardial injury in conscious dogs. Circ Res 1987;60:850–60.
15. Touchstone DA, Beller GA, Nygaard TW, et al. Effects of successful intravenous reperfusion therapy on regional myocardial function and geometry in humans: a tomographic assessment using two-dimensional echocardiography. J Am Coll Cardiol 1989;13:1506–13.
16. Smith PK, Stanley TE. Intraoperative contrast echocardiography: a direct approach to measure regional myocardial perfusion. Anesthesiology 1990;72:219–21.
17. Aronson S, Bender E, Feinstein SB, et al. Contrast echocardiography: a method to visualize changes in regional myocardial perfusion in the dog model for CABG surgery. Anesthesiology 1990;72:295–301.

120 ANESTH ANALG
1991;72:120–4

Clinical Reports

Caudal Morphine for Postoperative Analgesia in Infants and Children: A Report of 138 Cases

Robert D. Valley, MD, and Ann G. Bailey, MD

Key Words: PAIN, POSTOPERATIVE—pediatric. ANESTHESIA, PEDIATRIC—postoperative pain. ANESTHETIC TECHNIQUES, EPIDURAL—caudal morphine. ANALGESICS, MORPHINE.

Epidural narcotics have been shown to provide effective postoperative analgesia in pediatric patients (1–6). Caudal administration of morphine is perhaps the most widely used epidural narcotic technique in children. Although a number of studies have appeared in the literature describing dosing techniques, quality of analgesia, and side effects, these have all been from relatively small series of patients and have excluded patients under 1 yr of age (1–7). Since first utilizing caudal narcotics for postoperative analgesia at our institution we have performed more than 250 such blocks in infants as young as 1 day old. The purpose of this retrospective study is to report our early experience with this technique.

Methods

After obtaining Internal Review Board approval, the charts of all patients receiving caudal narcotics from July 1987 to July 1989 were reviewed. Age, weight, type of surgery, anesthetic technique, use of intraoperative narcotics, dose of caudal morphine, time and method of administration (single dose or via an indwelling catheter), adequacy of analgesia (as noted by nursing and physician assessments), time to first supplemental analgesic administration (narcotic administration of any kind by any route of administration based on nursing and physician assessments), and untoward events that might have been a result of the caudal narcotics were all recorded. Untoward events included pruritus, vomiting, urinary retention, excessive sedation, and respiratory depression. Urinary retention of more than 8 h duration or requiring bladder catheterization was considered significant. Respiratory depression was defined as apnea or episodes of arterial desaturation, bradycardia, or decreased respiratory rate that responded to repeated stimulation, intubation, or naloxone administration.

Only those charts with adequate documentation were included in the review. Charts were excluded if the time of initial caudal morphine administration, dosage used, timing of extubation, and at least initial analgesic effect were not documented. Statistical analysis was performed utilizing the Student's *t*-test for parametric data, the Spearman rank correlation for ordinal data, and the Fisher exact test for nominal data. A $P < 0.05$ was considered to be statistically significant.

Results

A total of 136 of 145 charts reviewed contained sufficient documentation to be included in the study. One hundred thirty-eight operations followed by use of caudal morphine for postoperative analgesia were included in the 136 charts. Sixty percent of the operations were abdominal, 38% were thoracic, and 2% were orthopedic. The age range of patients was from 1 day to 16 yr with a mean of 2.36 yr (Table 1). Fifty-four percent of patients were 1 yr of age or less

---

Received from the Departments of Anesthesia and Pediatrics, University of North Carolina School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. Accepted for publication August 13, 1990.

Address correspondence to Dr. Valley, Department of Anesthesia, University of North Carolina School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7010.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Results by Group

Group	Group total n (%)	Age (yr)	Weight (kg)	RD n (%)	CC n (%)	Intraoperative narcotics n (%)
All cases	138	2.36 ± 3.21	10.8 ± 9.5	11 (8)	14 (10)	83 (60)
No respiratory depression	107 (91)[a]	2.30 ± 3.37[b]	11.7 ± 10.1[c]	—	10 (9.3)	74 (60)
Respiratory depression	11 (9)[a]	0.87 ± 2.06[b]	5.4 ± 3.3[c]	—	4 (36)	5 (45)[e]
Caudal catheter	14 (10)	1.24 ± 1.76	8.6 ± 5.9	4 (28)[d]	—	0 (0)

RD, respiratory depression; CC, caudal catheter.

[a] Twenty patients not extubated by 2 h after caudal morphine administration were excluded.

[b] Incidence of respiratory depression in patients ≤1 yr was significantly greater than in those >1 yr ($P < 0.025$).

[c] Patients without respiratory depression weighed significantly more than patients with respiratory depression ($P < 0.039$).

[d] Incidence of respiratory depression in patients with a caudal catheter (28%) was significantly greater than in the patients without a caudal catheter (6%) ($P < 0.025$).

[e] Two additional patients received intravenous narcotics within 1 h of developing respiratory depression for a total of 7 (64%) of respiratory depression group receiving narcotics.

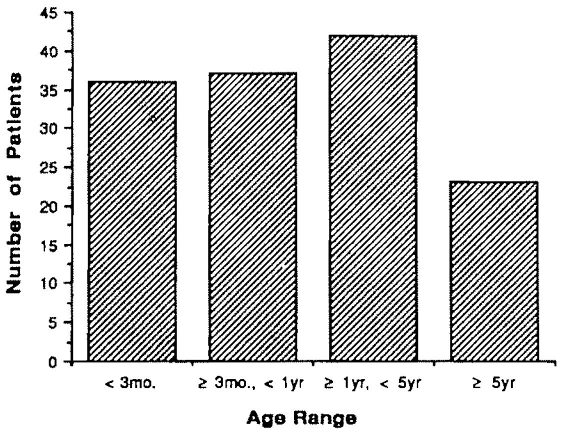


Figure 1. Age distribution.

at the time of surgery (Figure 1). Fifty-six percent of patients were male, and 44% were female.

Patients were anesthetized primarily with potent inhalation agents with or without nitrous oxide; all received muscle relaxants intraoperatively. Sixty percent of patients also received either intravenous fentanyl or alfentanil intraoperatively. Caudal morphine (Duramorph) was always administered at the end of the operative procedure. In all cases a dose of 0.07 mg/kg was used and was diluted with normal saline to a volume equal to or greater than 3 mL but less than 5 mL for patients weighing 5 kg or less, 5 mL for patients weighing more than 5 kg but less than 15 kg, and 10 mL for those weighing 15 kg or more. Entry of the needle into the caudal epidural space was confirmed by a negative aspiration test and a lack of resistance to injection or soft tissue swelling on injection. In 14 cases 20-gauge epidural catheters were threaded varying distances into the epidural space to assumed high lumbar or low thoracic levels. In 12 of these cases, catheters were placed before the operative procedure and were used intraoperatively for injection of 0.5–1.0 mL/kg of 0.25% bupivacaine. In the remaining two cases catheters were placed at the end of the operative procedure. Morphine was injected at the end of the operative procedure in patients with catheters in place.

Patients went either directly from the operating room to the intensive care unit or to the recovery room with subsequent discharge to a surgical ward or an intensive care unit. Patients less than 6 mo of age were cared for postoperatively in an intensive care unit. Heart rate and respiratory rate were continuously monitored in all patients for 12 h after the last dose of caudal morphine. Pulse oximetry monitoring was used in the recovery room and the intensive care unit. Naloxone was kept at each patient's bedside and immediate access to airway and ventilation equipment was provided.

Pain control was considered good to excellent in 81% (112) of cases, fair in 7% (10) of cases, and was poorly documented in the remaining 12% (16). The time interval to first supplemental analgesic administration was well documented in 121 cases and is shown in Figure 2. Seventy-five percent of patients did not need additional analgesics for the first 10 h after the initial caudal morphine administration. There was a trend toward a longer time interval to supplemental analgesia administration in patients given narcotics intraoperatively, although this did not achieve statistical significance.

The incidence of nonrespiratory side effects is listed in Table 2. Pruritus was specifically treated in two cases, once with diphenhydramine and once with a naloxone infusion. Vomiting was treated on six occasions, five times with rectal or intramuscular promethazine and once with intravenous droperidol. Eighty-two patients had urinary bladder catheters placed in the operating room. Of the remaining 56 patients, 28 had urinary retention, for which 19 had

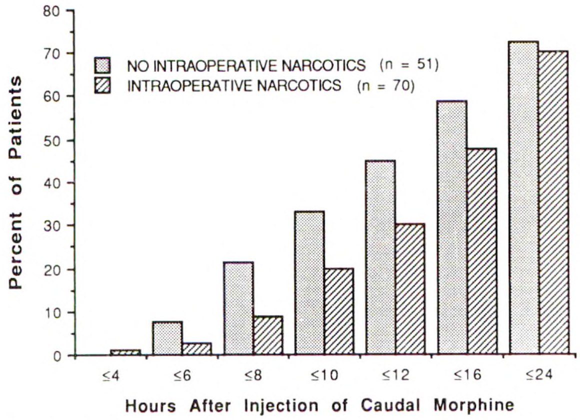


Figure 2. Percent of patients given supplemental narcotics (caudally, intravenously, or intramuscularly) as a function of time after he first caudal injection of morphine. Patients are divided into those who received intraoperative intravenous narcotics and those who did not.

Table 2. Nonrespiratory Side Effects

	n	Incidence (%)	Treatment required
Pruritus	4	3.1	2
Vomiting	10	7.7	6
Urinary retention	27	50.0	19
Excessive sedation	5	3.6	5

bladder catheterization performed postoperatively. Excessive levels of sedation were noted on five occasions. Three of these cases also involved respiratory depression. All five cases were treated with naloxone.

In 86% (118/138) of cases endotracheal tubes were removed within 2 h after the initial caudal injection of morphine. There were 11 cases of respiratory depression (Tables 1 and 3). Apnea was the sole presentation in two cases. In four additional cases, apnea was associated with either bradycardia, arterial desaturation with bradycardia, arterial desaturation with excessive sedation, or excessive sedation alone. The five patients without apnea had one or more episodes of arterial desaturation detected by pulse oximetry associated with one or more of the following: bradycardia (three), a decrease in respiratory rate (one), periodic breathing (one), and excessive sedation (one).

Ten of the 11 cases of respiratory depression occurred in infants 12 mo of age or younger ($P < 0.025$). Patients with respiratory depression weighed significantly less than those in whom respiratory depression did not occur ($P < 0.05$). All episodes of respiratory depression occurred in patients who had also received intravenous narcotics, except for four cases in patients with caudal catheters. The incidence of respiratory depression was significantly greater in patients with caudal catheters ($P < 0.025$) (Tables 1 and 3).

One case of respiratory depression occurred within 15 min of caudal injection of morphine and may have been secondary to intrathecal injection. The remaining 10 cases occurred at various times after caudal injection of morphine, although all were within 12 h with a mean time of 3.8 h (Table 3). The two cases of respiratory depression occurring after the first 6 h were preceded within 1 h by intravenous morphine administration. Excluding these two cases and the possible intrathecal injection, there was a significant correlation between age and time to the respiratory event (Spearman rank correlation of 0.84, $P < 0.01$).

Treatment of respiratory depression consisted of a bolus injection of naloxone in nine cases and was followed by a continuous infusion in six cases. One patient was managed with reintubation and mechanical ventilation, and the final patient required repeated stimulation only. All respiratory events were successfully managed. The naloxone boluses ranged from 5 to 20 μg/kg and the infusions from 2 to 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Pain control remained adequate in all cases except for patient 9, who required supplemental morphine after a naloxone bolus of 6 μg/kg.

Discussion

Although the effectiveness of caudal morphine for providing postoperative analgesia in children has been demonstrated in a number of studies, our series is unique in both its size and the number of infants included (1–8). Forty-two of our patients were younger than 6 mo of age and 15 were less than 1 mo of age. Caudal morphine provided effective postoperative analgesia in the majority of patients, with 75% of patients not requiring supplemental analgesics for the first 10 h after a single dose.

Altered respiratory drive has been shown to persist postoperatively for at least 22 h after the administration of epidural morphine in children, but there is only one case report in the literature of severe respiratory depression (4,9). The incidence of clinically important respiratory depression in our study was 8%, higher than that reported in adults (10). Ten of 11 cases in our study occurred in patients a year of age or less and weighing less than 9 kg.

The association of respiratory depression with age and weight may represent a maturational variability in the susceptibility to effects of caudally administered morphine similar to that reported with other

Table 3. Cases of Respiratory Depression

Patient	Age (yr)	Weight (kg)	Time to RD postcaudal (h)	Caudal catheter	IV narcotics?	IV narcotic type/dose[a]	IV narcotic time (h)[b]
1	0.08	3.7	1.50	Y	N	—	—
2	0.12	3.0	1.50	Y	N	—	—
3	0.20	4.8	2.00	Y	N	—	—
4	0.66	8.2	2.00	Y	N	—	—
5	0.01	3.8	1.25	N	Y	F/8	4
6	0.12	5.3	<0.5[c]	N	Y	F/5	1
7	0.17	2.9	0.50	N	Y	F/3	2.5
8	1.00	8.4	2.50	N	Y	F/4	4.5
9	7.00	13.5	5.25	N	Y	A/45	6
10	0.04	2.8	11.50	N	Y[d]	M/55	1
11	0.17	3.6	10.25	N	Y[d]	M/50	0.08
Average	0.87	5.45	3.83				
SD	2.06	3.32	3.93				

RD, respiratory depression; IV, intravenous; F, fentanyl; A, alfentanil; M, morphine.

[a] Dose given in μg/kg.

[b] Time between last intravenous narcotic and respiratory depression.

[c] Possible intrathecal injection.

[d] Given postoperatively (others given intraoperatively).

routes of morphine administration (11,12). Alternatively, rostral migration of the caudal morphine may vary with age or height. The average time to respiratory depression in our patients was only 3.8 h, and even less in the younger patients, whereas in adults the time to respiratory depression is usually longer.

Respiratory depression due to the central effect of systemically absorbed morphine would be an unlikely explanation for respiratory events occurring after the first hour because pharmacokinetic studies in children have demonstrated subanalgesic plasma levels within 1 h (4). High plasma levels of morphine may have accounted for the profound respiratory depression that occurred within the first 10–15 min after morphine administration to patient 6. Alternatively, this may have been due to inadvertent intrathecal administration of morphine.

All patients received the same 0.07-mg/kg dose of caudal morphine, a dose in the intermediate range of those reported in the literature (3,5,7). Krane et al. found a higher incidence of side effects in children receiving 0.1 mg/kg (versus two lower doses) and recommended a dose of 0.03 mg/kg (7). A lower dosage in our patients may have resulted in fewer side effects, including respiratory depression.

Excluding those of our patients with caudal catheters, all cases of respiratory depression occurred in patients who received supplemental intravenous narcotics. Rosen and Rosen reported on 16 children given 0.075 mg/kg of caudal morphine as well as liberal intravenous narcotic supplementation with no respiratory depression (5). Fewer patients as well as older patients (none less than 2 yr of age) may account for the absence of respiratory depression in their study.

The four patients with respiratory depression associated with caudal catheters in our study had all received intraoperative caudal local anesthetics. Residual sensory block from the local anesthetic may have reduced nocioceptive stimuli, unmasking any central nervous system depressant effects of the caudal morphine. How high the tip of the catheter lay in the epidural space also may have been a contributing factor. Morphine delivered through "high" catheters would result in a higher level of deposition and could affect both the time to onset and degree of centrally mediated effects.

The incidence of urinary retention was 51% in patients without bladder catheters in our study. Subsequent bladder catheterization was required in 70% of these cases. This is higher than the 27% and 29% incidences reported respectively by Krane et al. (7) and Attia et al. (4), but is similar to the 50% incidence reported by Glenski (3) after 0.1 mg/kg of epidural morphine. The incidence of vomiting (7.7%) as well as pruritus (3.1%) is low when compared with other reports and may reflect the retrospective nature of this study, the young age of many of our patients, and the fact that more than half of our patients had nasogastric tubes during the first 24 h postoperatively (4,7).

In summary, our early experience with caudal morphine in a large group of relatively young pediatric patients demonstrates its usefulness as a means of providing effective postoperative pain control. At the same time the clinician should be aware of the increased incidence of respiratory depression in patients under 1 yr of age, especially those patients that have received supplemental intravenous narcotics or have been dosed with caudal morphine via "high" caudal catheters.

References

1. Jensen BH. Caudal block post-operative pain relief in children after genital operations. A comparison between bupivacaine and morphine. Acta Anaesthesiol Scand 1981;25:373–5.
2. Shapiro LA, Jedeikin RJ, Shaley D, Hoffman S. Epidural morphine analgesia in children. Anesthesiology 1984;61:210–1.
3. Glenski JA. Postoperative use of epidurally administered morphine in children and adolescents. Mayo Clin Proc 1984;59: 530–3.
4. Attia J, Ecoffey C, Sandouk P, Gross JB, Samii K. Epidural morphine in children: pharmacokinetics and CO_2 sensitivity. Anesthesiology 1986;65:590–4.
5. Rosen KR, Rosen DA. Caudal epidural morphine for control of pain following open heart surgery in children. Anesthesiology 1989;70:418–21.
6. Krane EJ, Jacobson LE, Lynn AM, Parrot C, Tyler DC. Caudal morphine for postoperative analgesia in children: a comparison with caudal bupivacaine and intravenous morphine. Anesth Analg 1987;66:647–53.
7. Krane EJ, Tyler DC, Jacobson LE. The dose response of caudal morphine in children. Anesthesiology 1989;71:48–52.
8. Dalens B, Tanguy A, Haberer JP. Lumbar epidural anesthesia for operative and postoperative pain relief in infants and young children. Anesth Analg 1986;65:1069–73.
9. Krane EJ. Delayed respiratory depression in a child after caudal epidural morphine. Anesth Analg 1988;67:79–82.
10. Gustafsson LL, Schildt B, Jacobson K. Adverse effects of extradural and intradural opiates: report of a nationwide survey. Br J Anesth 1982;54:479–85.
11. Way WL, Costley EC, Way EL. Respiratory sensitivity of the newborn infant to meperidine and morphine. Clin Pharmacol Ther 1965;6:454–61.
12. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. Anesthesiology 1987;66:136–9.

ANESTH ANALG
1991;72:125–6

Too Much of a Good Thing: Uvular Trauma Caused by Overzealous Suctioning

Martin S. Bogetz, MD, Bradley J. Tupper, MD, and A. Christopher Vigil, MD

Key Words: COMPLICATIONS, SORE THROAT, TRAUMA—uvula.

Anesthesia-related trauma to the uvula has been reported to be caused by compression and injury of the uvula by the endotracheal tube (1), the oral airway (2), the nasal airway (3), or the laryngeal mask (4). Such injury can go unnoticed, even though the potential exists for life-threatening airway obstruction (1,5). We report four cases of uvular trauma believed to be caused by excessive suctioning of the pharynx.

Case Reports

During the spring of 1989, four adults complained of severe sore throat when queried by telephone the day after outpatient surgery. Each had the identical complaint of a severe, "raw" sore throat accompanied by gagging. Gagging was caused by a piece of "stringy" tissue hanging down the middle of the throat and touching the tongue. In addition to referring each patient to an otolaryngologist, we monitored the recovery of each person daily by telephone. Each was diagnosed as having uvular edema, presumed due to anesthesia-related trauma. All were treated conservatively and, within a few days, the sore throat resolved and the traumatized area became necrotic and sloughed off. All recovered completely.

Medical record review of these four cases indicated that each patient had a seemingly uncomplicated general anesthetic administered via an oral endotracheal tube. Specifically, these cases consisted of a 16-yr-old girl having temporomandibular joint manipulation, a 37-yr-old woman having a diagnostic laparoscopy, a 26-yr-old woman undergoing knee arthroscopy, and a 33-yr-old man having an open-reduction, internal-fixation of the wrist. All tracheal intubations were performed under direct vision and documented to be atraumatic. All endotracheal tubes met the Z-79 standard and were single-use. Oral and nasal airways were not used, and the only chemically disinfected item placed in the pharynx was a cleaned, rinsed, and dried laryngoscope blade. In each case, the pharynx was suctioned immediately before and after tracheal extubation using a Yankauer-type catheter (Pilling, Fort Washington, Pa.) attached to a wall-suction regulator (Ohio Vacuum Regulator, Ohio Medical Products, Madison, Wis.). These cases were not confined to one operating room or to the same anesthesia personnel.

Discussion

When our outpatient surgery facility recently opened, we were pleased that our new wall-suction equipment provided much stronger suction than had the equipment in a previous, older facility. Even though all suction pressure can be regulated in continuous gradation using equipment such as an Ohio Vacuum Regulator (Ohio Medical Products), because of historically poor suction, we decided to keep all regulators on the "FULL" setting to ensure robust suction.

Dorsch and Dorsch (6) define proper suction pressure as that which supports the weight of suction tubing held waist high. For a waist 95 cm from the floor at 30 ft above sea level, this is approximately −180 mm Hg. Our previous equipment provided a vacuum pressure of only −100 mm Hg. After reviewing the present four cases, we suspected that excessive suction pressure was responsible for the observed injuries. We measured vacuum pressure at the "FULL" setting and found it to be −500 mm Hg!

To test our hypothesis, that overzealous suctioning caused uvular trauma, one of the authors (A.C.V.) volunteered to have his pharynx anesthetized with 20% benzocaine and to undergo suctioning. On the "FULL" setting (−500 mm Hg), the Yankauer suction catheter stretched the uvula into its

---

Received from the Department of Anesthesia and The University of California, San Francisco Surgery Center, San Francisco, California. Accepted for publication August 28, 1990.

Address correspondence to Dr. Bogetz, UCSF Surgery Center A3, 400 Parnassus Avenue, San Francisco, CA 94143-0368.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

orifice from 1 cm away. When suction was regulated to −180 mm Hg, the uvula could not be suctioned into the orifice, even when touched directly by the Yankauer catheter. Since regulating our suction between −180 and −200 mm Hg, we have encountered no similar episodes of uvular edema.

In conclusion, the degree of negative suction pressure should be measured and regulated to an appropriate level. This is especially important when a new or refurbished operating room with a new wall-suction unit is put into service. When a sore throat after surgery specifically involves the uvula, overvigorous suctioning should be considered as a potential cause.

References

1. Ravindran R, Priddy S. Uvular edema, a rare complication of endotracheal intubation. Anesthesiology 1978;48:374.
2. Shulman MS. Uvular edema without endotracheal intubation (letter). Anesthesiology 1981;55:82–3.
3. Seigne TD, Felske A, DelGiudice PA. Uvular edema. Anesthesiology 1978;49:375–6.
4. Lee JJ. Laryngeal mask and trauma to uvula (letter). Anaesthesia 1989;44:1014–5.
5. Haselby KA, McNiece WL. Respiratory obstruction from uvular edema in a pediatric patient. Anesth Analg 1983;62:1127–8.
6. Dorsch JA, Dorsch SE. Understanding anesthesia equipment: construction, care and complications. Baltimore: Williams & Wilkins. 1984:409–10.

Letters to the Editor

Correct Application of the Shunt Fraction Calculation

Key Words: LUNG, SHUNT—calculation.

To the Editor:

Goldberg et al. (1) compared the hemodynamic and intrapulmonary shunt effects of labetalol and nitroprusside when used for inducing hypotension during major spinal surgery. The implication of their study is that a clinical advantage is conferred on the use of labetalol in place of nitroprusside for the controlled reduction of blood pressure. This conclusion was based in part on their findings that nitroprusside increased shunt but labetalol did not. The calculation of the shunt fraction has been incorrectly applied, however, which makes the validity of their conclusions equivocal.

First, in the Methods section, the authors state that a standard shunt formula was used for calculating the shunt fraction, *"one that includes V/Q contribution as well as true shunt."* The equation used,

$$Qs/Qt = (Cc_{O_2} - Ca_{O_2})\cdot 100/(Cc_{O_2} - Cv_{O_2}),$$

attributed to Berggren (2), was developed to calculate the oxygen deficit of arterial blood caused by nonventilating portions of the lung. In other words, the shunt fraction formula used by Goldberg et al. calculates the true shunt (atelectasis included); it does not include the contribution of $\dot{V}_A/\dot{Q}$ inequality. Also, to calculate the shunt fraction, subjects must breathe 100% oxygen for 15–20 min before the arterial and mixed venous blood samples are taken. This is necessary to minimize the effects of the uneven $\dot{V}_A/\dot{Q}$ normally present in the lungs (2,3). In the study of Goldberg et al. (1) the shunt fraction was not calculated after denitrogenation with 100% oxygen, which contradicts the principle on which the shunt fraction equation was developed. A review of these concepts has been published (3) to prevent just such misapplications of the shunt fraction calculation.

Even if one assumes that F_{IO_2}, cardiac output, and oxygen uptake did not play a role in the $\dot{Q}s/\dot{Q}t$ calculation, the clinical significance of the reported increase in $\dot{Q}s/\dot{Q}t$ from the prehypotensive baseline of 2.7 ± 1.2 to 6.0 ± 2.6 after 60 min of nitroprusside-induced hypotension (as shown in their Table 2) is questionable because both values are well within the normal limits of the shunt fraction. Thus, we believe that the results of the shunt fraction calculation obtained in this study do not justify the use of labetalol over nitroprusside.

Julio C. Cruz, MD
Departments of Anesthesiology and Physiology and Biophysics

Patricia J. Metting, PhD
Department of Physiology and Biophysics
Medical College of Ohio
3000 Arlington Avenue
Toledo, OH 43699

References

1. Goldberg ME, McNulty SE, Azad SS, et al. A comparison of labetalol and nitroprusside for inducing hypotension during major surgery. Anesth Analg 1990;70:537–42.
2. Berggren SM. The oxygen deficit of arterial blood caused by nonventilating parts of the lung. Acta Physiol Scand 1942;4(Suppl 11):1–92.
3. Cruz JC, Metting PJ. Understanding the meaning of the shunt fraction calculation. J Clin Monit 1987;3:124–34.

In Response:

We appreciate the comments expressed by Cruz and Metting on our recent article related to shunt calculation and feel a reply is in order.

Cruz and Metting have stated that our calculation of shunt fraction has been incorrectly applied because our patients were not breathing 100% oxygen, and that our calculation does not include V/Q mismatch thereby making our conclusions equivocal.

The calculation of shunt fraction at an F_{IO_2} of <1.0 has been a well-established practice for many years. Nunn (1) has stated that "pulmonary shunt during anesthesia seems to be much the same whether the patient breathes oxygen, nitrous oxide/oxygen mixtures, or nitrogen/oxygen mixtures."

Hedley-Whyte et al. (2) measured shunt at 100% F_{IO_2} and when room air was inspired to determine the contribution of uneven distribution of ventilation and perfusion in patients who had cardiac valve replacement. Douglas et al. (3) measured the fraction of pulmonary physiologic shunt flow (venous admixture) in postoperative mechanically ventilated patients at various inspired oxygen concentrations. At F_{IO_2} values of ≥0.7, there was a significant increase in venous pulmonary admixture to arterial blood

©1991 by the International Anesthesia Research Society

in all of the patients studied. A similar study was performed by Oliven et al. (4) in mechanically ventilated patients with similar findings. The latter two groups have suggested breathing 100% oxygen could, in itself, modify the pulmonary shunt in a manner that might be detrimental to some patients. Because our study period was up to 7 h in duration, we believed that it would not be good clinical practice to have patients breathing 100% oxygen for this period of time, thereby subjecting them to the possibility of increased absorption atelectasis and/or increased V_A/Q_C imbalance. Another factor in our decision to avoid utilizing an F_{IO_2} of 1.0 in determining Qs/Qt was that in studying drug effects on shunt, one logical consideration was that there could be an effect on hypoxic pulmonary vasoconstriction. Because hypoxic pulmonary vasoconstriction is operant in areas of low V/Q, it would have been inappropriate for us to eliminate this variable from our calculation of Qs/Qt by having patients breathe 100% oxygen.

We do not believe that our use of a clinically appropriate F_{IO_2} in the calculation of Qs/Qt is in conflict with Berggren (5) because the measurement conditions and measurement objective were different. Berggren studied spontaneously breathing subjects to determine the venous admixture to arterial blood caused by nonventilating parts of the lung. Our study, performed in anesthetized patients, sought to determine total physiologic pulmonary venous admixture to arterial blood.

In the article by Cruz and Metting (6), they describe the mathematical calculation of right-to-left intrapulmonary shunt utilizing a single-compartment physiologic lung model and not clinically anesthetized subjects. This model requires an inspired oxygen concentration of 100% to accurately reflect the true multicompartmental nature of the human lung. Pursuant to this, we disagree with their statement that our shunt formula is misapplied; however, we would readily agree that the single-compartment lung model is not applicable to our study population. This, therefore, supports our conclusion that the changes are most likely the result of the drug administered and not physiologic effects of inspired oxygen concentration or anesthesia on shunt (7).

Michael E. Goldberg, MD
Departments of Anesthesiology at
Jefferson Medical College
Thomas Jefferson University
111 South 11th Street
Philadelphia, PA 19107
and
Helene Fuld Medical Center
750 Brunswick Avenue
Trenton, NJ 08638

Joaquin Cantillo, MD
Department of Anesthesiology
Helene Fuld Medical Center

Marc Torjman, MEd
Stephen McNulty, DO
Said S. Azad, MD
Jefferson Medical College

References

1. Nunn JF. Respiratory aspects of anaesthesia. In: Applied respiratory physiology. Boston: Butterworth and Co., 1987:361.
2. Hedley-Whyte J, Corning H, Laver MB, Austen WG, Bendixen HH. Pulmonary ventilation-perfusion relations after heart valve replacement or repair in man. J Clin Invest 1965;44:406–14.
3. Douglas ME, Downs JB, Dannemiller FJ, Hodges MR, Munson ES. Change in pulmonary venous admixture with varying inspired oxygen. Anesth Analg 1976;55:688–93.
4. Oliven A, Abinader E, Bursztein S. Influence of varying inspired oxygen tensions on the pulmonary venous admixture (shunt) of mechanically ventilated patients. Crit Care Med 1980;8:99–101.
5. Berggren SM. The oxygen deficit of arterial blood caused by nonventilating parts of the lung. Acta Physiol Scand 1942;4(Suppl 11):1–92.
6. Cruz JC, Metting PJ. Understanding the meaning of the shunt fraction calculation. J Clin Monit 1987;3:124–34.
7. Goldberg ME, McNulty SF, Azad SS, et al. A comparison of labetalol and nitroprusside for inducing hypotension during major surgery. Anesth Analg 1990;70:537–42.

ECG Signals During Cardiopulmonary Bypass: Artifacts or Reality?

Key Words: ANESTHESIA, CARDIOVASCULAR—ECG interference. MONITORING, ELECTROCARDIOGRAPHY—interference.

To the Editor:

We read with interest the intriguing clinical report on electrocardiographic (ECG) artifacts during cardiopulmonary bypass (CPB) by Khambatta and colleagues (1). We have some relevant comments.

As a matter of historical interest, the authors are incorrect in stating that ECG interference during CPB had not previously been reported. Kaplan (2), for example, illustrated an ECG artifact attributed to CPB in 1981. More importantly, Soltys and colleagues (3) in 1983 not only pointed out the occurrence of such artifacts attributed to CPB, but offered a detailed explanation of this phenomenon.

Khambatta et al. also state that after cardioplegia was given it became impossible to distinguish the artifact from ventricular fibrillation. This reflects the fact that cardioplegia may not cause total electrical silence, i.e., electrical activity may still occur in some parts of the heart (4–6). A heart that is visually quiescent may still produce electrical activity. Hence, what the authors attributed to artifact may in fact have been patient's true electrical activity. Shutting off the pump for a few seconds may sort this out.

The authors go on to attribute generation of the artifact they observed to a build-up of static electricity on the polyvinylchloride perfusion tubing. This possibility may have been more completely evaluated by measuring the static charge with a static voltmeter. Furthermore, they discount the idea that the artifact was due to a piezoelectric effect because the artifact could be improved by spraying tap water or polyethylene glycol on the perfusion tubing. However, this in no way discounts the fact that the piezoelectric effect may in fact have been a major contributor to the generation of the observed artifact. Indeed, Soltys and colleagues (3) recognized the fact that the artifactual signal could be enhanced "by electrostatic charges caused by the friction of the rollers sweeping across the tubing." They also recognized that antistatic coatings would dramatically decrease the amplitude of the artifactual voltage. However, as Soltys et al. imply, these observations are not mutually exclusive: the piezoelectric effect may still be operative.

Also, an electrical artifact caused by the pump will be attenuated by a monitoring system with a high common mode rejection ratio. The common mode rejection capabilities of a monitoring system are degraded by the high electrode impedance and long lead wires frequently used for the operating room monitors. On rewarming during CPB, many patients become diaphoretic, and the electrode impedance can then increase substantially, thereby degrading the common mode rejection capabilities of the monitoring system. At this time, the artifacts will probably be recorded.

Finally, the signal produced by the CPB machine has been heretofore described as rhythmic with a frequency twice the revolution frequency of the roller heads when two heads are used (3). Theoretically, other types of signals could be produced if one views the polyvinylchloride perfusion tubing as a signal cable that is intermittently mechanically stressed by the roller pump heads. In this case, the signal so generated (triboelectric noise) may appear quite random (7).

In summary, some of what Khambatta et al. attribute to artifactual signals are in fact due to electrical activity of the heart. That portion that is truly pump artifact may still be due to a piezoelectric effect even though it is enhanced by electrostatic charge.

Bruce Kleinman, MD
Kamlesh Shah, MD
Uday Jain, MD, PhD
Department of Anesthesiology
Loyola University of Chicago
2160 South First Avenue
Maywood, IL 60153

References

1. Khambatta HJ, Stone JG, Wald A, Mongero LB. Electrocardiographic artifacts during cardiopulmonary bypass. Anesth Analg 1990;71:88–91.
2. Kaplan JA. The electrocardiogram in anesthesia. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1981:205.
3. Soltys ME, Bozarth RS, Tackel IS. Pump-related electrical interference during open heart surgery, AAMI technology update: electrocardiographic data acquisition and application for cardiac dysrhythmia monitoring. Arlington, Va.: AAMI, 1983:7–8.
4. Mullen JC, Khan N, Weisel RD, et al. Atrial activity during cardioplegia and postoperative arrhythmias. J Thorac Cardiovasc Surg 1987;94:558–65.
5. Jain U, Wallis DE, Rao TLK, Moran JF, Desari M. Correlates of postbypass conduction changes. Chest 1989;96:235S.
6. Ferguson TB, Smith PK, Lofland GK, Holman WL, Helms MA, Cox JL. The effects of cardioplegic potassium concentration and myocardial temperature on electrical activity in the heart during elective cardioplegic arrest. J Thorac Cardiovasc Surg 1986;92:755–65.
7. Ratz AG. Triboelectric noise. ISA Trans 1970;9:154–8.

In Response:

We thank Kleinman et al. for their interest in our paper (1). In the present day and age, with a plethora of textbooks and journals, it is not possible to have read them all, and we, like most authors, rely on computer-assisted literature searches provided by university libraries. The two references quoted by Kleinman and his associates, one in a 9-yr-old textbook and another in an unreviewed publication, did not show up on an extended search.

In our paper we demonstrated that the ECG artifacts appeared with the initiation of CPB and persisted till the CPB was discontinued. Therefore, the possibility of confusing the artifact with inadequate cardioplegia for establishing cardiac standstill does not arise. By the same token, an artifact coming on during rewarming, as alluded to by Kleinman et al., is of no consequence to our study and the suggestion about triboelectric noise is a non sequitur.

Finally, our work was not designed to differentiate between static electricity and the piezoelectric effect; that is a subject for another paper.

Hoshang J. Khambatta, MD
J. Gilbert Stone, MD
Alvin Wald, CCE, PhD
Department of Anesthesiology
College of Physicians and Surgeons
Columbia University
New York, NY 10032

Reference

1. Khambatta HJ, Stone JG, Wald A, Mongero LB. Electrocardiographic artifacts during cardiopulmonary bypass. Anesth Analg 1990;71:88–91.

Epidural Blood Patch: Why the Rapid Response?

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—blood patch.

To the Editor:

I read with interest the letter from Cook and Watkins-Pitchford (1), with its demonstration of the rapid in vitro clotting of blood when mixed with normal cerebrospinal fluid. The authors are to be congratulated on shedding new light on treatment by epidural blood patch.

I beg to take issue with them, however, on their suggestion that the rapid clotting might explain the nearly immediate relief of postspinal headache sometimes seen after treatment by epidural blood patch. It is widely accepted that postspinal headache is due to the reduction of cranial cerebrospinal fluid so that when the patient adopts the upright posture the brain moves slightly and causes traction on "headache-sensitive structures." An epidural blood patch then must effect a cure in a two-stage manner; first, the blood clot seals the hole in the dura, and, second, the brain's "cushion" of cerebrospinal fluid is replenished by the choroid plexuses in the ventricles—too slow a process (~0.5 mL/min) to explain the almost instant relief of headache sometimes seen after blood patching. It is more likely that this rapid relief is the result of the injected volume of blood raising the pressure in the epidural and spinal subarachnoid spaces so that cerebrospinal fluid is forced back inside the cranium and immediately restores the cushioning effect on the brain. The same effect can be produced by epidural injection of a bolus of saline in a patient with a postspinal headache, where the headache disappears before the injection has been completed.

This argument in no way detracts from the authors' findings. To those involved in performing epidural blood patching who have pictured a renewed leak of cerebrospinal fluid destroying a friable blood clot, it is reassuring to know that in these circumstances both coagulation is accelerated and a stronger clot is produced.

Len E.S. Carrie, MB, ChB, FFARCS, DA
John Radcliffe Maternity Hospital and
Nuffield Department of Anaesthetics
Headington, Oxford, OX3 9DU, United Kingdom

Reference

1. Cook MA, Watkins-Pitchford JM. Epidural blood patch: a rapid coagulation response. Anesth Analg 1990;70:567.

A Modest Proposal for Improved Humidifier Design

Key Words: EQUIPMENT, HUMIDIFIERS. COMPLICATIONS, ANESTHESIA CIRCUIT LEAK.

To the Editor:

The addition of a humidifier to an anesthesia circuit increases the potential for inadequate patient ventilation. Reports have described how various humidifiers have prevented low-pressure alarms from functioning (1), melted anesthesia circuits (2), and converted nonrebreathing systems into rebreathing ones (3). Recently, at our hospital, a humidifier failure caused a leak in a Mapleson D circuit that disrupted mechanical ventilation of a patient. Although the source of the leak was identified and ventilation of the patient was restored within 15 s without complication, the design of the humidifier hindered recognition of the component part's failure. The case report is as follows.

A 5-mo-old girl weighing 6.2 kg was brought to the emergency room with a perforated intussusception. While the attending pediatric anesthesiologist assisted with the fluid resuscitation of the infant preoperatively, the anesthesia resident assembled the components for a classic Mapleson D circuit with the addition of a Concha Therm III servo-controlled heater (catalog No. 380-80) to humidify the inspired fresh gases. After attachment to the humidifier and anesthesia machine, the circuit passed testing for low- and high-pressure leaks. Induction of anesthesia and tracheal intubation then proceeded without incident. Approximately 90 min into the operation, the pediatric ventilator's low-pressure alarm indicated that a circuit leak had developed. Attempts to ventilate manually were unsuccessful. Before this point, ventilation was uneventful with peak airway pressures 22–24 cm H_2O, $ETco_2$ 31–34 mm Hg, and O_2 saturation 100%. Visual inspection failed to locate an obvious patient disconnection. However, removing the humidifier from the circuit eliminated the leak and enabled ventilation to resume.

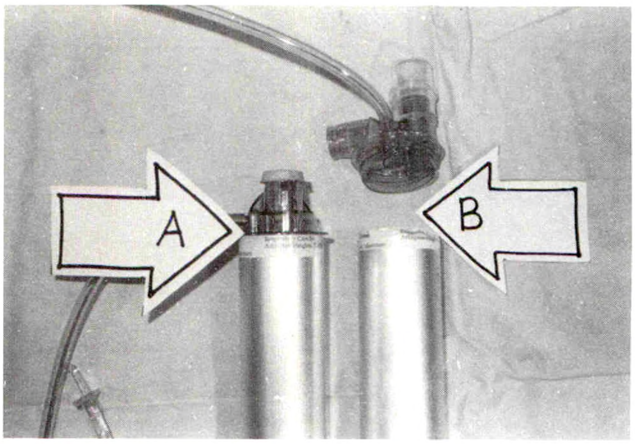


Figure 1. *Arrow A* points to the tape used to secure the lid to the base of the humidifier cartridge. *Arrow B* points to the failure of this tape to keep the lid attached to the base during use.

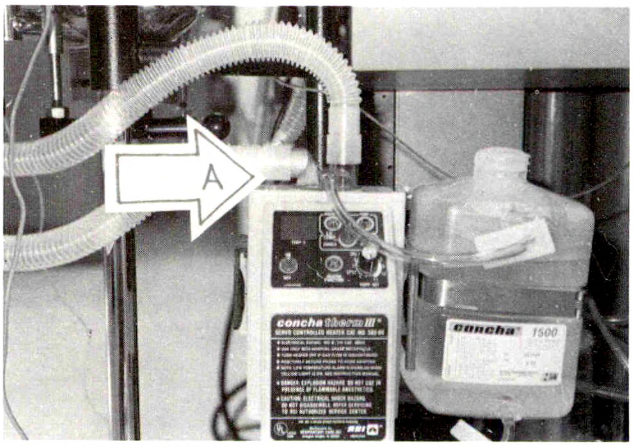


Figure 2. *Arrow A* points to where the taped portion of the humidifier cartridge is hidden within the humidifier base.

Close examination of the component parts of the humidifier assembly revealed that the lid of the standard "Concha-Column" humidifier cartridge (catalog No. 382-60) had become separated from its base. Specifically, as shown in Figure 1, the tape that the manufacturer (Respiratory Care Inc., Arlington Heights, Ill.) had used to secure the lid to the base of the column (arrow A) failed during use (arrow B). Because the manufacturer designed the taped portion of the column to rest within the humidifier base, this stress point is hidden from view (Figure 2, arrow A). If the manufacturer had made the column longer so that the taped portion was visible outside the humidifier base, then a lid that became detached would be readily identified. Even with this modification, we suggest removing the humidifier from the circuit at the first indication of an unexplained leak.

Eric L. Shampaine, MD
Mark Helfaer, MD
Department of Anesthesiology and Critical Care Medicine
Johns Hopkins University School of Medicine
600 North Wolfe Street
Baltimore, MD 21205

References

1. Slee TA, Pavlin EG. Failure of low pressure alarm associated with the use of a humidifier. Anesthesiology 1988;69:791–3.
2. Patil AR. Melting of anesthesia circuit by humidifier: another cause of "ventilator disconnect." Anesth Prog 1989;36:63–5.
3. Nimocks JA, Modell JH, Perry PA. Carbon dioxide retention using a humidified "nonrebreathing" system. Anesth Analg 1975;54:271–3.

Book Reviews

Lectures on Anesthetics and on Asphyxia

Claude Bernard, 1875. Translated by B. Raymond Fink. Park Ridge, Ill.: The Wood Library-Museum of Anesthesiology, 1989, 404 pp, $35.00.

The Wood Library-Museum of Anesthesiology has added a gem to its periodic reprinting of historically significant books in the history of the specialty. This book is especially important because it is the first English translation from the original French text published in 1875. Professor Fink has helpfully included notes summarizing Claude Bernard's life and role in the history of anesthesia. Through Bernard's work as a physiologist and pharmacologist, Fink suggests he may be the father of neuropharmacology for his careful distinction between the properties of "anesthesia," "narcosis" as the result of opiate narcotics, and hypnotics such as chloral hydrate.

The book includes a general introductory discussion on the role of the blood and the *milieu interieur* or internal environment, 10 lectures on anesthetics, six lectures on asphyxia based on studies of carbon monoxide, and a summary lecture attempting to unify the action of anesthetics on animals and plants.

The richness of Bernard's investigations includes observations on the actions of curare not introduced into clinical medicine for almost 90 years. The translation reads smoothly.

Who should purchase this book? Besides the obvious students of the history of anesthesia, those interested in the actions of narcotics, mechanisms of action of anesthetics, and the history of the scientific method. Teaching department libraries should provide all the historical reprints from the Wood Library. This volume would make a thoughtful gift for residents and would perhaps stimulate further inquiries into the history of the specialty.

A. Michael Broennle, MD
The Children's Hospital of Philadelphia
University of Pennsylvania
Philadelphia, Pennsylvania

Problems in Anesthesia, Volume 4, No. 2, June 1990: Thoracic Anesthesia

J. B. Brodsky, Guest Editor. Philadelphia: J. B. Lippincott Company, 1990, 180 pp, $30.00.

This monograph aims to be a concise update on recent clinical developments in the field of thoracic anesthesia and meets its set goals very satisfactorily. Each chapter is contributed by a different author, and the subjects covered are perioperative respiratory care, choice of anesthetic agent for thoracic surgery, isolation of the lungs, maximizing oxygenation during one-lung anesthesia, monitoring during thoracic surgery, anesthesia for special problems in thoracic surgery, anesthesia for pediatric thoracic surgery, managing postthoracotomy pain, and postoperative complications. At the start of each chapter the authors define "the problem" that will be addressed in that chapter.

Several of the chapters contain as much useful clinical information as that available in the major thoracic subspecialty texts. The chapter on postoperative analgesia gives a succinct review of all significant recent advances in this major problem area. It also details the author's preferred therapy and his or her reasons for the choices made. The chapter on postoperative complications covers relevant complications very thoroughly. The discussions of cardiac herniation and bronchopleural fistula are more complete and useful than those available in larger texts. Other chapters that are thorough while remaining concise and well-directed are those on anesthetic agent, monitoring, special problems, and pediatrics.

I have a few minor reservations about the way information is presented in some of the chapters. In some controversial areas more acknowledgment could have been made of the point of view that differs from the author's. For example, many anesthesiologists now routinely use fiberoptic bronchoscopy to survey the position of double-lumen endobronchial tubes, but this trend is dismissed as unnecessary and time-consuming.

Some management recommendations are made without warning the reader that these are based on theoretical or experimental evidence. An example of this is the advice to use aminophylline in preference to β_2-agonists in the chapter on oxygenation during one-lung anesthesia. However, in the past the clinical application of theoretical concepts (such as avoidance of volatile anesthetics and dependent-lung PEEP) during one-lung anesthesia has often not proven to be useful.

Unfortunately, most of the studies quoted regarding respiratory risk are drawn from nonthoracic surgical populations. There has been very little research done on the recovery of respiratory function after thoracotomy. However, there is some evidence to suggest that thoracic patients recover quite differently from other surgical populations. The reader should be warned that there is some

©1991 by the International Anesthesia Research Society

uncertainty in making extrapolations from other types of surgery.

These minor problems do not detract from this text's overall usefulness. There have been three major North American texts of thoracic anesthesia produced in the past decade. These are generally too large for a clinician to read cover to cover. This monograph fills a gap between these major subspecialty texts and the limited information on thoracic anesthesia available in the comprehensive anesthesia texts. The monograph is designed for the practicing clinician, and he or she will be well rewarded for the time invested in reading it.

P. D. Slinger, MD, FRCPC
Department of Anaesthesia
Montreal General Hospital
McGill University
Montreal, Quebec, Canada

Emergency Airway Management

Michael S. Gorback, ed. Philadelphia: B. C. Decker, 1990, 183 pp, $29.95.

The prospect of intubating a critically ill patient under emergency conditions fills most beginning anesthesia residents and many experienced anesthesiologists with fear, especially if the situation is not routine. In this book, Dr. Gorback outlines various approaches to airway management and intubation that may be useful under such difficult circumstances. The book grew out of lecture notes and "handouts" prepared by Dr. Gorback for anesthesia residents assigned to the Emergency Airway Management Service at Duke University Medical Center. It is clearly and simply written in outline format. Included are discussions of airway anatomy, patient assessment, and equipment. Basic airway management with bag, mask, and/or adjuvant devices and oral and nasal endotracheal intubation are well described. Additional chapters include fiberoptic intubation, considerations in the pediatric patient, pharmacologic aids to intubation, and specific pathophysiologic states that might make establishing an airway more difficult.

The recommendations made are based mostly upon the author's personal opinion and experience, supplemented by contributions from Dr. Edmond C. Bloch (Pediatric Airway Management), Dr. J. Michael Plavcan (Applied Airway Anatomy), and Dr. Charles B. Watson (Fiberoptic Intubation). When views are controversial, differing viewpoints are given and adequately referenced. Each chapter contains an annotated bibliography that is a mixture of classic and recent articles. Illustrations abound in the book. These are mostly photographs (including seven color plates) rather than line art. The photographs, especially of the airway, demonstrating views during laryngoscopy, and of cadaver prosections, demonstrating anatomic relationships, are superb. The color plates of laryngoscopic views of the airway are excellently reproduced. Unfortunately, the reproduction of the black-and-white photographs could have been much better. A few errors also seemed to slip by the proofreaders (Figures 6.4b and 6.5 on pp. 96–7, are reversed, for example).

Although the book is an excellent introduction to emergency airway management for the novice, it is not meant to be an exhaustive reference work. Each subject is only briefly considered and some topics, such as AIDS and equipment cleaning and sterilization, are not mentioned. The index is too brief, and it is inadequately cross-referenced. Nevertheless, this book is recommended highly, especially to anesthesia residents who are beginning the lifelong and humbling task of becoming competent in emergency airway management. It is an excellent primer, written clearly and with a sense of humor, and based on common sense. Most importantly for the overly tired resident, it is easily read in an afternoon and the outline format and many photographs help drive the important concepts home.

William E. Hurford, MD
Harvard Medical School
Department of Anesthesia
Massachusetts General Hospital
Boston, Massachusetts

Outpatient Anesthesia

Paul F. White, ed. New York: Churchill Livingstone, 1990, 520 pp, $65.00.

Perhaps no other area in anesthesia has grown as rapidly in the past decade as outpatient anesthesia. Dr. Paul White, an established leader in the field, has edited this comprehensive text which is intended to be "a resource for anesthesiologists, both in practice and training, as well as other physicians, nurses, and health care professionals involved in ambulatory surgery care."

There is an impressive array of 28 contributors, many of whom are distinguished academicians. The 21 chapters cover virtually all aspects of ambulatory anesthesia, ranging from administrative, legal, and personnel issues to anesthetic techniques and patient selection. Recognizing that ambulatory anesthesia must deal with social, economic, and regulatory issues, Dr. White has devoted approximately 25% of the text to this area. In addition there is comprehensive coverage of standard anesthetic topics, such as preoperative assessment, premedication, general anesthesia, monitoring techniques, and regional anesthesia.

Almost all of the authors have tailored their discussions to outpatient care, which is what makes this book so useful. For example, given that a large proportion of outpatients undergo procedures with conscious sedation, the topic of monitored anesthesia care, although not a "flashy" subject, is covered extensively. Realizing that outpatient anesthesia is still evolving, several authors have wisely avoided dogma. For instance, the chapter on preoperative assessment of pediatric outpatients clearly states what is known and what remains speculative. Fortunately, the author provides practical information and guidelines based on available data. In addition, important, provocative, and often uncomfortable issues are dealt with squarely. For example, regarding rapid assessment of outpatients, the author states, "Insurance companies and the US government are dictating medical care, and this has resulted in many marginal patients being forced to receive their care in an ambulatory setting. Insurance companies and the federal government have set the policy, and the anesthesiologist is responsible for the consequences."

Included among the many excellent chapters are the editor's (which is a thorough monograph on outpatient anesthesia) and the chapters on pediatrics, regional anesthesia for outpatients, preoperative assessment, economic issues, and current controversies. Although some of the chapters sound quite familiar and suffer from anecdotal information or a "cookbook" approach, on balance most of the authors are intent on presenting objective data in an informative and educational manner. This book is highly recommended as a reference for any anesthesiologist who cares for outpatients on a regular basis.

Barbara S. Gold, MD
University of California
San Francisco, California

Clinical Monitoring

Carol L. Lake. Philadelphia: W. B. Saunders Co., 1990, 831 pp, $105.00.

Patient monitoring is a major part of the clinical practice of anesthesiology. This text is written for the clinical trainee seeking discussions of the methods and devices available for performing specific monitoring functions. Twenty-nine authors have contributed 22 chapters that are organized into seven sections. These sections include cardiovascular monitoring, respiratory monitoring, maternal-fetal monitoring, computerized monitoring, monitoring of the nervous system, anesthesia machine monitoring, and biochemical monitoring. The introduction considers the history of monitoring and includes recent concepts of cost-effective monitoring and standards of monitoring.

Each chapter reviews the applied physiology that is relevant to clinical care and that forms the basis for monitoring. The physical principle of specific technology is reviewed, and clinical indications and complications are discussed. The explanations of the physical basis of clinical measurement are often introductory and may not satisfy the reader who wishes to understand a specific method in detail. Investigations of the accuracy of the measurement techniques in clinical practice are summarized; however, there is little critical interpretation of individual study methods or conclusions. A practitioner responsible for specifying anesthesia equipment purchases will not find enough practical detail to guide such decisions. The text focuses on monitoring methods that are in current clinical practice with little attention to research techniques or emerging technology for clinical care. Future directions in monitoring in anesthesia receive only brief attention.

This text has few typographical errors and is well illustrated and indexed. The text contains 1922 literature citations with 16% from 1987 to the present and 27% from 1983 to 1986. As in many multiauthor texts, there is some redundancy of presented material and the degree of detail varies from chapter to chapter. In general the text is well edited and functions well as a whole. Trainees in anesthesia will find this text a valuable source of information for integrating concepts of applied physiology with clinical monitoring practice. Experienced clinicians looking for detailed critical discussions of monitoring technology, future trends, or information to guide the purchase of equipment will find the focus of the text less suitable.

Lawrence C. Siegel, MD
Stanford University School of Medicine
Stanford, California

Anesthesiology and Vascular Surgery, Perioperative Management of the Vascular Surgical Patient

Mark P. Yeager and David Glass, eds. East Norwalk, Conn.: Appleton & Lange, 1990, 379 pp, $69.95.

This book is comprised of five parts that have been subdivided into 15 chapters covering virtually all aspects concerning patients undergoing vascular surgery. The editors' goal was to present an accurate and comprehensive text that is also easy to use and concise. The text is written in a practice-oriented rather than a problem-oriented style.

The two chapters in Part 1 are written by four vascular surgeons and cover the pathophysiology of vascular disease, surgical techniques, and decision making. This reviewer found the chapter on pathophysiology to be both comprehensive and informative. The chapter covering surgical techniques and decision making does not cover lesions of the arch or ascending aorta. Nonoperative techniques such as the use of lasers and atherectomy devices are also not covered. The explanation of various surgical procedures is complemented by numerous figures and illustrations that should prove useful to residents and those less familiar with vascular surgery.

Part 2 deals with preoperative evaluation and preparation of the vascular surgery patient. The chapter on diagnostic procedures, written by radiologists, covers techniques ranging from Doppler ultrasound and magnetic resonance imaging to angiography. This chapter will be useful and informative for most readers. Chapter 4 is written by three French anesthesiologists and addresses the areas of cardiovascular, pulmonary, and renal risks and assessments. Although there are 100 references, many of which are later than 1985, this chapter could have been expanded to be more comprehensive. Chapter 5 covers monitoring techniques. In this reviewer's opinion, the cardiovascular monitoring section is well written and informative; however, the sections on pulmonary and renal function monitoring are more superficial in their coverage.

Part 3 covers anesthesia for various surgical procedures. The chapter on carotid endarterectomy and, to a lesser degree, the chapter on infrarenal aortic reconstruction are less comprehensive than those appearing in some other texts and are somewhat less extensively referenced. The chapter on thoracic aortic surgery has a number of useful figures and covers a relatively new concept of cerebrospinal fluid drainage for spinal cord protection. The sections dealing with monitoring and actual anesthetic management and options are, although covering almost all pertinent considerations, somewhat less comprehensive. Chapter 9 deals with peripheral vascular surgery; a discussion of the use of lasers and atherectomy devices is absent. Chapter 10 addresses organ protection, and almost all aspects are touched upon, including the relatively new concept of the use of intrathecal papaverine for spinal cord protection. A discussion of the role of magnesium in central nervous system protection, dysrhythmias, or control of blood pressure is absent.

Part 4 concerns itself with the postoperative period. Virtually all aspects of postoperative consideration and potential complications are addressed. This reviewer would like to have seen a number of sections expanded such as those on coagulopathies, fluid management, renal function, pulmonary function, and pain management. Some of the new agents such as aprotinin and desmopressin are not covered.

Part 5 covers evolving changes in our practice. The role of monitoring complements an earlier chapter in Part 3, and the chapter on prevention of cerebral ischemia complements chapters in Part 3 dealing with organ protection and carotid and thoracic aortic surgery. The chapter on prevention of cerebral ischemia is comprehensive, clear, extensively referenced (229), and contains a very informative section in central nervous system monitoring. The final chapter deals specifically with the role of regional anesthesia in vascular surgery. This chapter is current, with a number of references in 1989, and addresses the controversies surrounding the use of regional anesthesia for vascular surgery. Topics covered include cardiovascular effects, endocrine responses, pain management, and neuroaxial complications.

In summary, this text gives the reader an extensive body of information on vascular anesthesia, presented by surgeons, radiologists, and anesthesiologists. The chapters vary in quality, and there is an expected degree of redundancy. Discussions of some of the newer modalities or agents such as use of lasers, atherectomy devices, desmopressin, and aprotinin, and the role of magnesium, are absent, but otherwise the text is generally informative and comprehensive. This text is recommended to anesthesia residents, to anesthesia departments, and to those involved with vascular surgery as an addition to their libraries.

John A. Youngberg, MD
Department of Anesthesiology
Tulane Medical Center
New Orleans, Louisiana

Regional Anesthesia for Intraocular Surgery: Ophthalmology Clinics of North America, Volume 3, No. 1

K. Zahl and M. A. Meltzer, eds. Philadelphia: W.B. Saunders Co., 1990; 129 pp, $76.00 annual subscription for four issues.

The editors of this greatly needed volume, an anesthesiologist and an ophthalmologist, have provided a real service to both specialties. The topics selected are well covered with virtually no duplication, a common fault with multiauthored works, and include preoperative evaluation and choice of anesthesia, anatomy, pharmacology of local anesthetics, pharmacology of general anesthetics, anesthesia for pediatric ophthalmic surgery, special blocking techniques, and complications of regional anesthesia.

The diagrams are excellent and although borrowed from standard ophthalmology texts are of great value to anesthesiologists who otherwise would not have ready access to them. The color plates on pages 74 and 75 are superb, and one can only wish they were enlarged and spread over more pages. Likewise, the photographs of techniques for retroperibulbar blocks are well done and quite helpful to those wishing to become more familiar with this technique. It is unfortunate that the chapter on the pharmacology of intravenous agents is marred by numerous misspellings and a few inaccuracies.

This is a book that should be in the library of every anesthesiologist who deals at all with ophthalmic surgery. I think the publisher would be well advised to reprint it as a single volume (rather than a part of the series subscription) and to make it available to anesthesiologists. If not, I would recommend you borrow this volume from an ophthalmologist friend.

John J. Leahey, MD
Department of Anesthesia
Willis Eye Hospital
Philadelphia, Pennsylvania

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Marino PL. *The ICU Book*. Philadelphia: Lea & Febiger, 1991, 713 pp, $39.50.

Muravchick S. *The Anesthetic Plan: From Physiologic Principles to Clinical Strategies*. St. Louis: Mosby Year Book, 1990, 425 pp, $45.00.

Tuma RF, White JV, Messmer K, eds. *The Role of Hemodilution in Optimal Patient Care*. San Francisco: W. Zuckschwerdt Verlag, 1990, 146 pp.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
65th CONGRESS — March 8–12, 1991
Marriott Rivercenter • San Antonio, Texas

MEETING REGISTRATION, HOTEL RESERVATION, SCIENTIFIC MEETING INFORMATION: Will be mailed in December to all IARS members. (IARS members outside of North America who plan to attend the meeting will receive this material by airmail upon request.) Non-IARS members should request information from the **NEW IARS OFFICE ADDRESS:** Suite 140, 2 Summit Park Drive, Cleveland, OH 44131. Tel: (216) 642-1124.

MEETING SCHEDULE: **Registration:** Friday, March 8, 1–6 PM
Scientific Program: Saturday–Tuesday, March 12
Exhibits: Saturday–Monday, March 11

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture, Sunday, March 10,
"Anesthesia Journals: The Backbone of the Specialty — Past, Present, and Future"
Nicholas M. Greene, MD, Emeritus Professor of Anesthesiology,
Yale University School of Medicine, New Haven, Connecticut,
and Editor-in-Chief, *ANESTHESIA and ANALGESIA*

REVIEW COURSE LECTURES:

MD Abel, MD — Transesophageal Echocardiography — Its Real Role in Clinical Anesthesia
PG Barash, MD — Preoperative Assessment of the Patient With Cardiac Disease
DR Bevan, MD, and RD Miller, MD — Anesthesia Literature — A Critical Approach to Reading and Writing
DR Cook, MD — Anesthetic Management of Neonatal and Infant Surgical Emergencies
MJ Cousins, MD — The Injury Response and the Prevention of Postoperative Pain
BG Covino, MD — New Techniques in Regional Anesthesia
N Ellison, MD — Blood Transfusions — When and What?
M Finster, MD — Newer Trends in Obstetric Pain Relief
AB Froese, MD — Ventilator-Related Lung Injury — New Concepts
TJ Gal, MD — Anesthesia and Gas Exchange — HPV, FRC, CC, and Other Acronyms
DE Longnecker, MD — The Case for Perioperative Blood Pressure Control
M Maze, MD — Alpha-2 Agonists and Anesthesia
SC Nicolson, MD — Perioperative Fluid Management in the Pediatric Patient
WS Nimmo, MD — Alternate Modes of Drug Delivery
GW Ostheimer, MD — Contemporary Issues in Obstetric Anesthesia
RG Pearl, MD — Sepsis — Etiology and Management
DS Prough, MD — Anesthetic Management of the Patient With Head Trauma
C Prys-Roberts, DM — Total Intravenous Anesthesia — Assessment of Adequacy
JG Reves, MD — Physiology of Cardiopulmonary Bypass
JJ Savarese, MD — Does the Choice of Muscle Relaxant Really Matter?
S Slogoff, MD — Outcome Studies in Anesthetic Data — A Perspective
NT Smith, MD — Perioperative Anesthetic Data — What to Do With It?
RK Stoelting, MD — Allergy and Anesthesia
JH Tinker, MD — How?/Should?/Does? Malpractice Litigation Affect Anesthetic Practice?
PF White, MD — Monitored Anesthesia Care — Appropriate Use of Adjuvant Drugs
MP Yeager, MD — The Role of Regional Anesthesia in Improving Surgical Outcome

PANELS

ANESTHESIA MACHINES AND VENTILATORS — Saturday, March 9, 8:00 AM
NW Lawson, MD, Moderator; JJ Andrews, MD, J Condurso, North American Drager, and JB Biondi, Ohmeda
YOU, THE ANESTHESIOLOGIST IN COURT — A MOCK MEDICAL MALPRACTICE TRIAL
(Based on an actual case) — Saturday, March 9, 1:00 PM
DH Morrow, MD, Moderator; Hon. D Hittner, F Stein, MD, TP Sartwelle, Esq., RJ Swift, Esq.
MEDICAL LITIGATION: PROBING THE DEPTHS — Sunday, March 10, 8:00 AM
PG Fine, MD, Moderator; AR Nelson, MD, JA Jacobson, MD, L Andrews, JD
LEGISLATIVE UPDATE — LUNCHEON SESSION — Sunday, March 10
BP Stephenson, MD, and AC Lang, representing American Society of Anesthesiologists
EMERGENCY AIRWAY MANAGEMENT — Monday, March 11, 8:00 AM
MS Gorback, MD, Moderator; JL Benumof, MD, EJ Krane, MD, CB Watson, MD

CLINICAL AND RESEARCH PRESENTATIONS

More than 300 clinical and research papers will be presented in concurrent oral and poster sessions.

REGISTRATION • CME CREDIT • AIR TRAVEL • HOTELS

FEES: IARS Members — $275 ($300 on site) Non-members — $450 ($475 on site)
IARS Educational Members — No fee Non-member residents — $50 (with certification)

CME CREDIT: Category 1 — 27 hours

DELTA SPECIAL AIRFARES: Discounted fares for IARS meeting registrants. For details call 1-800-241-6760, File No. P-0095.

HOTELS: The Marriott Rivercenter will serve as headquarters hotel where all meetings and exhibits will be held. A limited number of additional rooms have been blocked at the St. Anthony. Reservation forms to be included in the December mailing must be used to obtain the discounted rates of IARS meeting registrants.

A Guide for Authors

Manuscripts should be sent to:

Nicholas M. Greene, MD
Editor in Chief
Anesthesia and Analgesia
Yale University School of Medicine
333 Cedar Street, New Haven, CT 06510

Editorial Policies

Anesthesia and Analgesia, the oldest publication for the specialty of anesthesiology, is the official voice of the International Anesthesia Research Society. It publishes original articles, clinical reports, technical communications, review articles, and letters to the editor.

All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Only one copy of an article not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a covering letter that must include a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar, work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1988;108: 258–65 and *Lancet* 1982;284:1766–70.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, from parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

General

☐ Original articles describe in 3000 words or less clinical or laboratory investigations.

☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.

☐ Technical communications are papers that deal with instrumentation and analytic techniques.

☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.

☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double spaced, and a title and three copies must be provided.

☐ Type manuscripts on white bond paper, 216 by 279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 25 mm (1 in.) using double spacing throughout.

☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

☐ Submit three copies of manuscript and figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

☐ Authors should keep copies of everything submitted.

Title Page

☐ The title page should contain the title of the article, which should be concise but informative;

☐ A short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified;

☐ First name, middle initial, and last name of each author, with highest academic degree(s); each listed author must a) have participated in the work to the extent that he or she could publicly defend its contents; b) have read the manuscript prior to its being submitted for publication; and c) be prepared to sign a statement to the effect that he or she has read the manuscript and agrees with its publication;

☐ Name of department(s) and institution(s) to which the work should be attributed;

☐ Disclaimers, if applicable;

☐ Name and address of author responsible for correspondence about the manuscript;

☐ Name and address of author to whom requests for reprints should be addressed, or a statement that reprints will not be available from the author;

☐ The source(s) of support in the form of grants.

Abstract and Key Words

☐ The second page should carry an abstract of not more than 150 words. (Abstracts are not needed for Clinical Reports.)

☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.

☐ Define all abbreviations except those approved by the International System of Units.

☐ Key (indexing) terms: Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article and that may be published with the abstract.

Text

☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion.

☐ Case reports, reviews, and editorials do not require the above sections.

☐ *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

☐ *Methods:* Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are

©1991 by the International Anesthesia Research Society

not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.

☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data.

☐ *Units of measurement:* Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in **SI units** with, if desired, present conventional metric units in parentheses.

References

All references must be available to all readers. Cite only references to books and articles or abstracts published in peer reviewed *Index Medicus* journals. Abstracts appearing only in programs of meetings are not acceptable, nor are abstracts more than five years old.

☐ Number references consecutively in the order in which they are first mentioned in the text, except in review articles when references may be arranged alphabetically.

☐ Identify references in text, tables, and legends by arabic numbers (in parentheses, on line)

☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus.*

☐ The titles of journals must be abbreviated according to the style used in *Index Medicus.*

☐ References must be verified by the author(s) against the original documents.

☐ Examples of correct forms of references are given below:

Journals:

1. *Standard journal articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.) You CH, Lee KY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1980;79:311–4.
2. *Personal author(s) books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
3. *Chapter in a book*
   Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

Tables

☐ Type each table double spaced on a separate sheet. Do not submit tables as photographs.

☐ Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading.

☐ Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use lower-case italicized letters in alphabetical order.

☐ Do not use internal horizontal or vertical rules.

☐ Cite each table in the text in consecutive order.

☐ If data are used from another published or unpublished source, obtain permission and acknowledge fully.

Illustrations

☐ Submit three complete sets of figures. Figures should be in black and white only and professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Note: Art work of published articles will not be returned.

☐ Instead of original drawings, roentgenograms, or other material send sharp, unmounted, glossy black-and-white photographic prints, usually 127 by 173 mm but no larger than 203 by 254 mm.

☐ Each figure must have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them by using paper clips. Do not bend figures.

☐ Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with the background.

☐ Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.

Legends for Illustrations

☐ Type legends for illustrations double spaced starting on a separate page, with arabic numerals corresponding to the illustrations.

☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

Abbreviations

☐ The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement. Avoid abbreviations in the title.

☐ Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 5th ed. Bethesda, Maryland: Council of Biology Editors, 1983; and
2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

Exclusive Publication Statement

☐ The principal author of all materials submitted for publication (except letters to the editor) must include in a covering letter a statement to the effect that none of the material in this manuscript has been published previously nor is any of this material currently under consideration for publication elsewhere.

☐ Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

Classified Advertising

LOUISIANA
Anesthesiologist. Board-certified or -eligible anesthesiologist to fill clinical faculty positions at a University Medical Center. The position responsibilities include administration of anesthesia, teaching of residents, and supervision of CRNAs. Encouragement will be given to initiate or participate in research. Faculty rank and salary will be commensurate with experience. Louisiana State University Medical Center, School of Medicine in Shreveport is an affirmative action/equal opportunity employer. Send curriculum vitae to D. Richard Davis II, MD, Chairman, Department of Anesthesiology, LSU Medical Center, P.O. Box 33932, Shreveport, LA 71130-3932.

468H/A

PACIFIC NORTHWEST
Position available for board certified or soon to be board certified anesthesiologist. Send CV and date available to Box 472H/A.

472H/A

FULL-TIME ANESTHESIOLOGIST
BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to 1415 18th Street, Lake Charles, LA 70601.

497I/B

ILLINOIS
Large, well-established, single-specialty group of anesthesiologists seeks additional BC/BE anesthesiologists. Challenging opportunity for those interested in a broad-based practice. All surgical subspecialties represented. Minimal OB and pain management. Early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 61614.

511J/C

CALIFORNIA
From time to time faculty positions as an Assistant Professor become available in the *Regular Professorial Series (Tenure Track)* in the UCLA Department of Anesthesiology. Candidates are required to show evidence or promise of research productivity and scholarly writing. Other requisites include clinical and teaching skills; commitment to discovery; eligibility for a California Medical License; ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

526J/C

CALIFORNIA
Faculty positions in the *Clinician-Teacher* Academic Professorial Series in the UCLA Department of Anesthesiology are available. We are interested in all anesthesia subspecialties. Requisites include eligibility for a California Medical License and ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

527J/C

ANESTHESIOLOGISTS, MISSOURI
Anesthesiologists needed at assistant, associate, and professor levels. Must be board certified or board eligible. Duties include patient care, resident and medical student teaching, and research. Positions available at the University of Missouri-Columbia Health Sciences Center. Interested applicants send Curriculum vitae to G.W.N. Eggers, Jr., MD, Professor and Chairman, Department of Anesthesiology, University of Missouri Health Sciences Center, Columbia, MO 65212.

529K/A

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY
The Department of Anesthesiology of Columbus Children's Hospital is expanding its fellowship program. Positions are currently available for a 1-year fellowship in pediatric anesthesiology. Children's Hospital of Columbus, Ohio is a 313-bed general pediatric institution with a surgery caseload of 13,000–14,000 cases per year. All pediatric surgical specialities are represented with large case loads in pediatric neurosurgery and cardiovascular surgery. Regional anesthesia in infants and children along with acute/chronic pain management experience is available. An active transplantation service is present. Opportunity for research is provided under the guidance of a full-time director of research. Inquiries should be submitted to J. David Martino, MD, Chairman, Department of Anesthesiology, Columbus Children's Hospital, Columbus, OH 43205.

531K/D

CALIFORNIA
Anesthesiology, Pain Management Fellowship, UC Irvine. The University of California, Irvine, Department of Anesthesiology is accepting applications for CA4 fellowship positions in Pain Management. The rapidly expanding Pain Management Center at UC Irvine offers extensive clinical experience and education in all aspects of acute and chronic pain. With the addition of six new Pain Management faculty, there is extensive emphasis on the teaching of regional anesthetic techniques, invasive and noninvasive chronic pain regimens, and involvement of other disciplines. The clinic for chronic pain provides services to all types of pain patients, and the large University Medical Center is an excellent medium for the use of standard and sophis-

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announcements, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum 1/4 page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.25 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $17.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia* Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

icated acute pain modalities. In addition to developing clinical expertise in pain management, our fellows get involved in research projects with the help of a full-time research assistant. Six-month or one-year fellowships are available. MD degree and California license are required. Send curriculum vitae and three references to Carl A. Hess, MD, Director, Pain Management Center, Department of Anesthesiology, University of California, Irvine, 101 City Drive South, Route 81A, Orange, CA 92668; (714) 634-6437. The University of California, Irvine is an equal opportunity employer.

541K/A

FELLOWSHIP—CARDIAC ANESTHESIA
The Department of Anesthesia, University of Toronto is accepting applications for a 12-month fellowship beginning January 1, 1991 or July 1, 1991. Experience and training will include all aspects of cardiac anesthesia, ICU, and/or clinical research for 2000 open heart patients per year. Candidates must have completed a recognized anesthesia training program and be eligible for academic licensure. Inquiries, CV, and three references should be addressed to Sallie J. Teasdale, MD, Director of Cardiac Anesthesia, The Toronto Hospital, 200 Elizabeth Street, Toronto, Ontario, Canada, M5G 2C4.

542L/A

MISSOURI
The Department of Anesthesiology of St. Louis University School of Medicine is seeking board-qualified or certified full-time faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110–0250; telephone (314) 577-8750.

544L/D

CRNA
Opening for CRNA in a 250-bed teaching medical center with significant trauma volume. Located 100 miles north of Los Angeles in an "All-American" city of 175,000, and close to many excellent recreational areas. Compensation and benefits are competitive. Quality of life exceptional. For more information, contact Human Resources, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305; (805) 326-2643, FAX (805) 326-2229.

546L/A

CHAIRPERSON—DEPARTMENT OF ANESTHESIA
Kern Medical Center seeks a Chairperson, Department of Anesthesia, who will form a corporation and independently contract for anesthesiologists' services to the Medical Center. The Corporation is to engage six (6) full-time anesthesiologists including the Chairperson. Kern Medical Center is a 240-bed teaching institution with a large emergent, OB and Neuro volume serving as a trauma center. Excellent quality of life is offered in an "All-American" city with a moderate cost of living, warm climate, and varied recreational activities.

Requires board certification, a California license, and five or more years of clinical practice experience. Chairperson will be eligible for a UCLA faculty appointment. Send resumes to Anesthesia Search Committee, Room C-150, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305.

547L/B

ANESTHESIOLOGIST
Board eligible/certified anesthesiologists with California license to join group contracting services for Kern Medical Center, a busy teaching institution in growing area of 350,000 and an "All-American" city. If interested, submit resume to Search Committee, Room C150, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305.

548L/B

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, DIRECTOR OF RESIDENT AFFAIRS
Faculty position available for board-certified/eligible anesthesiologist. Must have at least 5 years of postgraduate training, including research or other clinical training. As Director of Resident Affairs, incumbent will act as liaison between faculty and residents, and the Chairman in relation to all aspects of residency program. Incumbent will be responsible for the efficient running of the resident office and will be responsible for recruitment, education, and daily operation of the residency program. Under its umbrella, this position will also be responsible for medical students and postdoctoral fellows. Duties also include patient care, resident and medical student teaching, and research or specialized clinical activity. Special areas of interest may include any aspect of anesthesia. California medical license required. Send correspondence, curriculum vitae and list of professional references to Ronald D. Miller, Professor and Chairman, Department of Anesthesia, Box 0648, Room C-455, 521 Parnassus Avenue, University of California, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Employer.

555L/A

ANESTHESIOLOGIST(S)
The Department of Anesthesia, University of California, San Francisco, seeks candidates at the assistant or associate level(s) for teaching and clinical responsibilities at the Veterans Administration Hospital in San Francisco. Candidates must have training in clinical cardiovascular research. The ongoing research studies are multidisciplinary and multicenter, addressing perioperative ischemia and morbidity. The University of California is an Equal Opportunity Affirmative Action Employer. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, or, Dennis Mangano, MD, PhD, Professor, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-0648.

556L/A

MAINE
BC or BE MD to join group of three MD anesthesiologists and four CRNAs, in the practice of anesthesia, intensive care and respiratory care. Phone (207) 622-1959 from 8:30 AM to 3:30 PM. Write to Chief of Anesthesia, Kennebec Valley Medical Center, 6 East Chestnut Street, Augusta, ME 04330.

560L/E

BE/BC ANESTHESIOLOGIST
SW PA, 300-bed, modern community hospital to work with 3 MDs and CRNAs. Competitive starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to box 561L/B.

561L/B

NEW YORK
CA 3 or 4 fellowship positions at Memorial Sloan-Kettering Cancer Center beginning July 1991. Straight clinical and clinician–investigator opportunities available in critical care medicine, pain management, and anesthesia for thoracic surgery. Send CV and summary of career goals to Mary E. Fischer MD, Director of Anesthesia Training, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

563L/B

DIRECTOR OB ANESTHESIA
Board-certified, 1-year OB fellowship, several years practice with administrative experience. Call (301) 365-7580. Write Director of Anesthesia, Columbia Hospital, 2425 L Street NW, Washington DC 20037.

565L/A

ANESTHESIOLOGIST

BC/BE to join group of 10 MDs with CRNAs in a large hospital located in a pleasant midwestern community on the Great Lakes. Busy practice covering all major surgical subspecialties plus respiratory/ICU involvement and OB. Excellent starting salary and benefits package leading to early partnership. Send CV to Associated Anesthesiologists of Toledo, Inc., 2409 Cherry Street, Suite 4, Toledo, OH 43608.

566A/C

ANESTHESIOLOGY

Come join our medical team! We are a 640-bed medical center located in the heart of Columbus, Ohio. Our hospital offers a full range of anesthesia services including OB, neuro, pain management, and open heart. Over 14,000 anesthesia procedures performed annually. Our service area exceeds 1.5 million people and Columbus is one of the fastest growing areas in the midwest. Our community offers a wide range of cultural opportunities and is currently ranked as the nation's tenth most desirable place to live. We have all the advantages of a major metropolitan area, including access to a noted medical university; or, if you prefer, a chance to unwind with a visit to the quiet and scenic hills of the Ohio Valley. Competitive package and benefits. Address inquiries/forward curriculum vitae to Jim Christian, Grant Medical Center, 111 South Grant Avenue, Columbus, OH 43215; (614) 461-3346.

567AB

LOCUM TENENS

Anesthesiologist, MD. Experienced, AMG, board certified. Will consider permanent situation. Licensed: MO, KS, CO, IA, NC, SC, PA, VA, IL, IN, KY, OH, TN; others pending. PO Box 1176, Kings Mountain, NC 28086; (704) 739-4683 Office, (704) 739-1917 Home.

568A/C

ANESTHESIOLOGISTS

Oklahoma City; 500-bed hospital has positions available for two (2) BC/BE anesthesiologists, each to commit 50% of time to obstetrical services. Obstetric facility is new 19,000-ft unit, two (2) operating rooms with new equipment, postsurgical recovery, 14 LPRP rooms with central and bedside monitoring. Level I and II deliveries, well-trained staff. Hospital provides salary, benefits, and malpractice. Reply Box 569AB.

569AB

CA III POSITIONS IN ANESTHESIOLOGY

The Department of Anesthesia at New England Medical Center Hospitals, Boston, Massachusetts (Tufts University) is accepting applications for CA III positions in adult cardiac anesthesia. This will be a 6-month rotation specializing in all aspects of cardiac anesthesia beginning July 1991 and January 1992. Include CV with letter. Reply to Box 570AB.

570AB

OHIO

Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

571A/F

CRNA AND ANESTHESIOLOGIST

The Dayton Veterans Affairs Medical Center is actively recruiting for anesthesiologists and CRNA anesthestists. Anesthesiologists may be board certified or board eligible. CRNAs must have current licensure. Interested candidates should send CV to Lloyd G. Phillips, MD, Acting Chief of Surgery, VA Medical Center, 4100 West Third Street, Dayton, OH 45428, (513) 262-2150. An Equal Opportunity Employer.

572A

SOUTHERN CALIFORNIA

Olive View Medical Center, a UCLA-affiliated Los Angeles County hospital, is seeking academically qualified anesthesiologists. Board certified or in process required. Training in OB, pediatrics, or neuro desired. No OH or trauma. Please send CV with three references to Anesthesia Search, Department of Anesthesiology, Olive View Medical Center, 14445 Olive View Drive, Sylmar, CA 91342. Equal Opportunity Employer.

573A/C

ILLINOIS, CHICAGO

Anesthesiologist BC/BE to join expanding group practice limited to outpatient anesthesia. Excellent opportunity for growth. Send CV to Marc Sloan, MD, 25 East Washington, Suite 300, Chicago, IL 60602.

574A/F

MEDICAL DIRECTOR

Anesthesiologist for AAAHC approved outpatient surgical center in Philadelphia suburbs. Board certification and administrative experience required. Applicants please send curriculum vitae to Chestnut Hill Anesthesia Associates, 8815 Germantown Avenue, Philadelphia, PA 19118.

575A

ANESTHESIOLOGISTS

Temple University School of Medicine has full-time faculty positions available for board-eligible anesthesiologists with training in a subspecialty area (obstetrical anesthesia, cardiac anesthesia, or neuro-anesthesia and/or critical care). Faculty rank will be commensurate with experience. Duties include patient care, teaching, and research. Send curriculum vitae to Christer Carlsson, MD, Chairman, Department of Anesthesiology, Temple University School of Medicine, Broad and Ontario Streets, Philadelphia, PA 19140. An Equal Opportunity/Affirmative Action Employer.

576AB

UTAH

The University of Utah seeks board-certified and/or board-eligible anesthesiologist for faculty position with subspecialty training in pediatric anesthesia. Experience in clinical or basic science research is required. Position commensurate with experience. Send curriculum vitae to K.C. Wong, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. Equal Opportunity/Affirmative Action Employer. Closing date: January 31, 1991 or until suitable candidate is found.

577A

CRNA for large regional mid-Michigan hospital. Competitive salary and excellent fringe benefits, including fully paid health and malpractice insurance. Most specialties with high percentage OB/GYN. Ideal Great Lakes location for the sportsperson. Contact Vickie Henige, Saginaw General Hospital, 1447 North Harrison, Saginaw, MI 48602; (517) 771-4502.

578AB

PEDIATRIC ANESTHESIA

The Department of Anesthesia, Faculty of Medicine, University of Manitoba and the Health Sciences Centre invite applications for a contingent, geographical full-time position of Section Head, Pediatric Anesthesia in the Children's Hospital, Winnipeg, Manitoba.

Experience in administration, research, and intensive care are highly desirable. Candidates must have Senior Specialty qualifications in anesthesia in the country of current practice and must be eligible for registration with the College of Physicians and Surgeons of Manitoba. Certification in anesthesia by the Royal College of Physicians and Surgeons of Canada is preferred. Salary and academic rank will be commensurate with experience and qualifications.

The University of Manitoba encourages applications from qualified women and men, including members of visible minorities, aboriginal people, and persons with disabilities. The University provides a smoke-free work environment. In accordance with Canadian Immigration requireents, priority will be given to Canadian tizens or permanent residents.

Please forward applications and curricu m vitae to Dr. D. Biehl, Chairman, Search ommittee, Department of Anesthesia, niversity of Manitoba, St. Boniface Genral Hospital, 409 Tache Avenue, Winipeg, Manitoba R2H 2A6.

579A

ANTED?

ffable anesthesiologist to join progressive n-loving department in central Vermont rea. Locate in the mountains. See the aves. 4 MD, 1 CRNA group. We do pain ur way. DO IT NOW—send CV to Chairan, Department of Anesthesia, c/o Central ermont Hospital, PO Box 547, Barre, VT 5641. A limited time offer. Respond now!!

580A/D

LINOIS

eeking three BC/BE well-trained anestheiologists to join 12 physicians and 15 RNAs in a busy group practice that inludes cardiothoracic, neuro, neonatal, and B at a 650-bed hospital with an academic ffiliation. Subspecialties considered, espeially cardiac, pediatric, and obstetrics. Exellent salary and benefits. Send CV to uentin A. Pletsch, MD, St. John's Hospial, 800 East Carpenter, Springfield, IL 2769.

581AB

NESTHESIOLOGIST: SUNNY SOUTH

mmediate opening for clinical BC/BE aneshesiologist at the University of Alabama at irmingham, Department of Anesthesiolgy. Desire to do clinical research and esident teaching necessary. Salary cometitive with private practice situations. imited night call. Generous benefit packge. Located in downtown Birmingham; ity rated "America's most livable city" by he United States Conference of Mayors in une 1989, and rated by *Newsweek*, February 989, as "one of the nation's top ten 'hot ities'." Please contact Simon Gelman, MD, hD, Department of Anesthesiology, The niversity of Alabama at Birmingham, 619 outh 19th Street, Birmingham, AL 35233, 205)934-4696.

583AB

ALIFORNIA

he UCLA Department of Anesthesiology as openings for faculty with experience in nesthesia for organ transplantation. Reqisites include clinical and teaching skills; ligibility for a California medical license; BA certification or in process. Address orrespondence with names of five refernces and curriculum vitae to Stuart F. ullivan, MD, Department of Anesthesiolgy, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

584A/F

THE UNIVERSITY OF NEW MEXICO

A reorganized, expanding Department of Anesthesiology in the "Land of Enchantment" has seven immediate openings at the Assistant and Associate Professor levels. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to James C. Scott, MD, Associate Professor and Acting Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106, (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

585A/F

MISSOURI

BC/BE anesthesiologist to join a large hospital-based group practice with CRNAs in the St. Louis area. The position includes rotation for OB coverage and administering anesthesia for a variety of surgical procedures. State-of-the-art equipment. Excellent salary and a competitive benefit package including two days off after call. Call or send CV to Ali Eldin, MD, North County Anesthesia Associates, Christian Hospital Northeast, 11133 Dunn Road, St. Louis, MO 63136; (314) 355-2300, ext. 5426.

586A

ILLINOIS

Anesthesiologist BC/BE sought for MD/CRNA team at progressive 350-bed southern Illinois hospital which includes cardiothoracic. CV to Box 587AC.

587AC

PEDIATRIC ANESTHESIOLOGY

Nemours Children's Clinic, Jacksonville, Florida, is seeking two pediatric anesthesiologists. Candidates must be BC/BE in anesthesiology. A pediatric anesthesiology fellowship or the equivalent in experience is desirable. These physicians will be offered an academic appointment of assistant/associate professor with the University of Florida College of Medicine. Interested applicants should send curriculum vitae to Dr. Dennis R. Stone, Chairman, Search Committee, Nemours Children's Clinic, 807 Nira, Jacksonville, FL 32207; (904) 390-3600.

Academic status is offered by The University of Florida, An Equal Opportunity-Affirmative Action Employer with whom Nemours is Affiliated.

Recruiting deadline: 2/1/91.

589A

PAIN EVALUATION AND TREATMENT INSTITUTE, UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE

The Pain Evaluation and Treatment Institute is a comprehensive, university-based interdisciplinary facility dedicated to the highest standards of clinical services, education, and research. The interdisciplinary staff consists of physicians, psychologists, physical therapists, occupational therapists, and nurses.

The Pain Institute is seeking a flexible and innovative Pain Specialist to serve as a full-time member of a physician group currently consisting of anesthesiologists and a physiatrist. This unique position involves program development, supervision of fellows and residents, clinical research, as well as direct clinical work with diverse pain populations.

Current clinical programs at the Pain Institute include an Acute Pain Service, Head and Facial Pain Clinic, Pain Rehabilitation Program, Cancer Pain Service, Regional Anesthesia Clinic, Back Injury Clinic, and a Work Performance Assessment and Rehabilitation Program. Research associated with each of these programs and services is currently underway.

Prior experience and academic achievement in pain medicine is desirable. The successful candidate must have the desire and ability to work with an interdisciplinary clinical and research team. MD degree and licensure or license eligibility in Pennsylvania required. Academic rank and salary will be commensurate with qualification.

Send CV and three reference letters to Michael C. Brody, MD, Medical Director, Pain Evaluation and Treatment Institute, University of Pittsburgh School of Medicine, Baum Boulevard and Craig Street, Pittsburgh, PA 15213.

591A

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:

The unique feature of these tutorials is the small group size. The personalized format with a maximum of four students in a session allows your performance to be evaluated throughout the session and permits you to raise questions for discussion. Tutoring for the written and oral exams are given separately. The sessions are held in San Francisco and New York and are given in blocks of 3 days. FOR THE WRITTENS, essential test-taking skills are taught for dealing with multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, mock orals are practiced using the guided case discussions which meet the Board's stated objectives. All students will receive study programs for use following these sessions. CALL 415-321-1117.

505I/B

---

(800) FAST-GAS

The number that hundreds of hospitals nationwide have called for permanent and

temporary anesthesia services. The number that thousands of anesthesia professionals have called to secure permanent and temporary positions nationwide. Bay Area Anesthesia, Inc. 1-800-327-8427 for years of professional anesthesia service.

473H/A

J. STEPHENS MAYHUGH AND ASSOCIATES LOCUM TENENS ANESTHESIA SERVICES
Providing top-quality CRNAs to meet your specific needs. Our CRNAs are screened to assure quality in performance as well as personal stability. License verification, curriculum vitae, references procured by us, AANA recertification, malpractice verification are supplied to you. Call 1-800-426-2349 any time.

552L/E

A WEEKEND OF PRACTICE ORAL EXAMS
Practice exams, not lectures. We are the original course in this format. 20 hours Category I CME credit, two board-certified instructors, 12 students maximum. Tampa, February 1–3 and March 1–3; Dallas, March 22–24; Denver, April 5–7. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480.

557L/A

LOCUM-TENENS ANESTHESIOLOGISTS
Earn up to $40,000 more per year than agencies pay. Don't work for an agency. Work for yourself as I do. For details, send name and address to Dr. Monroe, 7035 Highway 6 South, Suite 175-B, Houston, TX 77083.

538KAB

DON'T FAIL THE WRITTEN BOARDS/ITE
New 1990 edition of practice questions (including past board remembered questions), answers, test-taking techniques, and more. We want to help you pass. Order the original, MEDTEXT call 1-800-695-6301 24 hours a day.

590A/F

INDEX TO ADVERTISERS

- Academic Physician Services
  - *Recruitment* A30
- Albany Medical Center
  - *Recruitment* A29
- Anaquest
  - *Stadol* . . . . . A15 thru A16
- Arrow International
  - *Medical Division* A8
- Augustine Medical
  - *Bair Hugger* A6
- Burron Medical Inc.
  - *Perifix* . . . . . Cover 4
- Georgetown University Medical Center
  - *Symposium* A29
- Janssen Pharmaceutica
  - *Alfenta* A4
  - *Sufenta* A25
- Kaiser Permenente
  - *Recruitment* A30
- Medfusion, Inc.
  - *Syringe Pump* . . . . . Cover 3
- Mercury Medical
  - *2001 Laryngoscope* A14
- Northern Health Systems
  - *Computer System* A27
- Organon Pharmaceuticals
  - *Norcuron* . . . . . Cover 2, A1–A2
- Osler Institute
  - *Course* A12
- Preferred Physicians Mutual
  - *Insurance* A13
- Professional Seminars, Inc.
  - *Seminar* A14
- Stuart Pharmaceuticals
  - *Diprivan* . . . . . A17 thru A23
- University of Pittsburgh
  - *Recruitment* A30
- West Virginia University
  - *Recruitment* A29, A30

Advertising Office: Pharmaceutical Media, Inc., 440 Park Avenue South, 14th Floor, New York, New York 10016. Telephone: (212) 685-5010

ISSN 0003-2999
Volume 72, Number 2, February 1991

Acc 7 7/93

Anesthesia and Analgesia

CENTRAL LIBRARY

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

Norcuron®

vecuronium bromide) for injection

efore prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

ONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

ARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVI-ION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT IGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, RTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN UST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the yasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral rve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle laxants.

RECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity actions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated ith histamine release are unlikely to occur.

enal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in atients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric atients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-ective surgery, a lower initial dose of Norcuron® should be considered.

ltered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous ates resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be creased.

epatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping ith the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage ecommendations in patients with impaired liver function.

ong-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate echanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted uring attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum ntibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, ypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms onsistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-isk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support echanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIM-LATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

evere Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or entilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as orcuron®.

alignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially atal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be ccompanied by adequate anesthesia or sedation.

rug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration f Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the tubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular lock with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate ome of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs nd Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use f Norcuron® and other competitive muscle relaxants in the same patient.

nhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. otentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may e the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution

†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug µg/kg/min	Patient Weight – kg 40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

References:

1. Morris RB, Cahalan MK, Miller RD, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983;58:438-440.
2. Lowry KG, Mirakhur RK, Lavery GG, et al: Vecuronium and atracurium in the elderly: A clinical comparison with pancuronium. *Acta Anaesthesiol Scand* 1985;29:405-408.
3. Miller RD, Rupp SM, Fahey MR, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron*. Amsterdam, Excerpta Medica, 1983, pp 124-126.
4. Bell CF, Hunter JM, Jones RS, et al: Use of atracurium and vecuronium in patients with oesophageal varices. *Br J Anaesth* 1985;57:160-168.

Organon

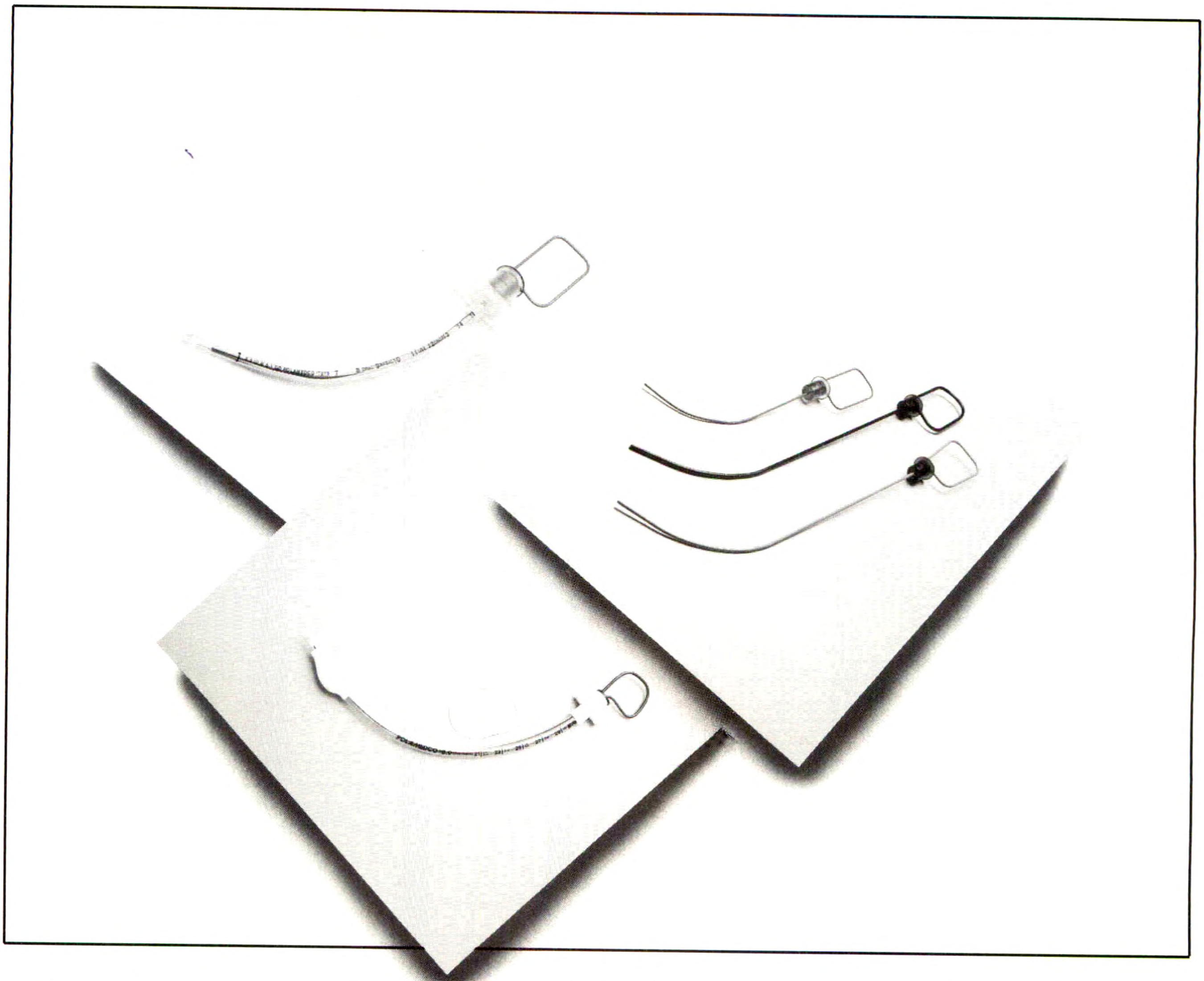
ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Manufactured for ORGANON INC.
By BEN VENUE LABORATORIES, INC. • BEDFORD, OHIO 44146
or by
ORGANON INC. • WEST ORANGE, NEW JERSEY 07052

PTD. IN USA-440, 441

©1989 ORGANON INC.

5310117



Polamedco's Slick Stylette... Insures Greater Safety During Intubation

Unique design facilitates first-attempt intubations with minimal risk and trauma.

The SLICK® Stylette ET Tube Guide from Polamedco offers a long track record of safety, speed, and convenience.

☐ The SURELOC® Stop prevents unintentional stylette advancement beyond distal end of the ET tube.

☐ Stylette is easily lengthened or shortened by positioning the SURE-LOC Stop to the correct location. No lubrication is required.

☐ Three sterile, color-coded sizes accommodate neonatal-infants, pediatric or small adults, and adults.

☐ The SLICK Stylette fits 2.0mm to 10mm ET tubes.

Also available: Cuffed and uncuffed ET Tube/Stylette combinations; sterile, disposable and ready for immediate use at a considerable cost saving.

The SLICK Stylette: an inexpensive answer to greater safety, greater peace of mind.

For complete information and pricing contact:

Polamedco, Inc.
8295 So. La Cienega Blvd.
Inglewood, CA 90301-1521

Call toll free: (800) 227-7578
In California call (213) 417-3901

POLAMEDCO INC®

Anesthesia and Analgesia

Journal of International Anesthesia Research Society

Suite 140, 2 Summit Park Drive, Cleveland, Ohio 44131-2553 Telephone: (216) 642-1124

LIBRARY UNIVERSITY

Editorial Board

Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada
Phillip O. Bridenbaugh, MD, Cincinnati, Ohio
Mieczyslaw Finster, MD, New York, New York
Thomas J. Gal, MD, Charlottesville, Virginia
Paul R. Hickey, MD, Boston, Massachusetts
Edward D. Miller, Jr, MD, New York, New York
Walter S. Nimmo, MD, BSc, FRCP, FFARCS, Edinburgh, Scotland
Nathan L. Pace, MD, Salt Lake City, Utah
Richard J. Palahniuk, MD, Minneapolis, Minnesota
Ronald G. Pearl, MD, PhD, Stanford, California
Donald S. Prough, MD, Winston-Salem, North Carolina
Joseph G. Reves, MD, Durham, North Carolina
John J. Savarese, MD, New York, New York
John H. Tinker, MD, Iowa City, Iowa
Barbara E. Waud, MD, Worcester, Massachusetts

Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Manuscripts should be addressed to: RONALD D. MILLER, MD, *Anesthesia and Analgesia*, University of California, San Francisco, 521 Parnassus Avenue, Room C-450, San Francisco, CA 94143-0648. For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 655 Avenue of the Americas, New York, NY 10010; prices on request.

All articles published in this Journal become the property of the International Anesthesia Research Society. This journal has been registered with the Copyright Clearance Center, Inc. Consent is given for the copying of articles for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay through the Center the per-copy fee stated in the code on the first page of each article for copying beyond that permitted by the US Copyright Law. If no code appears on an article, the author has not given broad consent to copy, and permission to copy must be obtained directly from the author. This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works.

On-line text is available through BRS Colleague, 8000 Westpark Drive, McLean, VA 22102; telephone (800) 289-4277.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, Edward D. Miller, Jr, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K. C. Wong, MD, PhD. Emeritus Trustees are: Paul R. Dumke, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Morris J. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1991 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year, in all other countries $110.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited by anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, and students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: International Anesthesia Research Society, Suite 140, 2 Summit Park Drive, Cleveland, Ohio 44131-2553.

Subscription information for 1991 applying to non-IARS members: Institutions, $140.00; nonmember individuals, $100.00. Outside of the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico, $55.00 for surface airlift to Europe, $75.00 for surface airlift to Japan, and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical sciences, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

This journal is printed on acid-free paper.

Shield against surgical stress
SUFENTA®
(sufentanil citrate) Injection CII
For longer more stressful procedures
5 ml
SUFENTA® CII
(SUFENTANIL CITRATE)
INJECTION
NDC 50458-050-05

As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

References: 1. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology. 1982;56:112-118. 2. Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg. 1985;64:897-910. 3. Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology. 1986;65:A516. Abstract. 4. Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stresss associated with worse outcome? Anesthesiology. 1987;67:A1. Abstract. 5. Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology. 1987;66:130-135.

Predictable control of stress responses from induction through recovery

***REDUCES** stress response to intubation and surgical stimulation*^{1,2}

***PROVIDES** intraoperative hemodynamic stability*

***CONTROL** of the stress response is associated with less postoperative morbidity*^{3,4}

***MAINTAINS** postoperative analgesia with faster recovery of respiratory drive*^{5}

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.
DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.
INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.
CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.
Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.
Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.
Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.
ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.
DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

world leader in anesthesia research

JANSSEN
PHARMACEUTICA

Piscataway, NJ 08854

March 1986, March 1987
U.S Patent No. 3,998,834
7618505-M

© Janssen Pharmaceutica Inc. 1989 JPI-SU-025A-R

Anesthesia and Analgesia

Contents

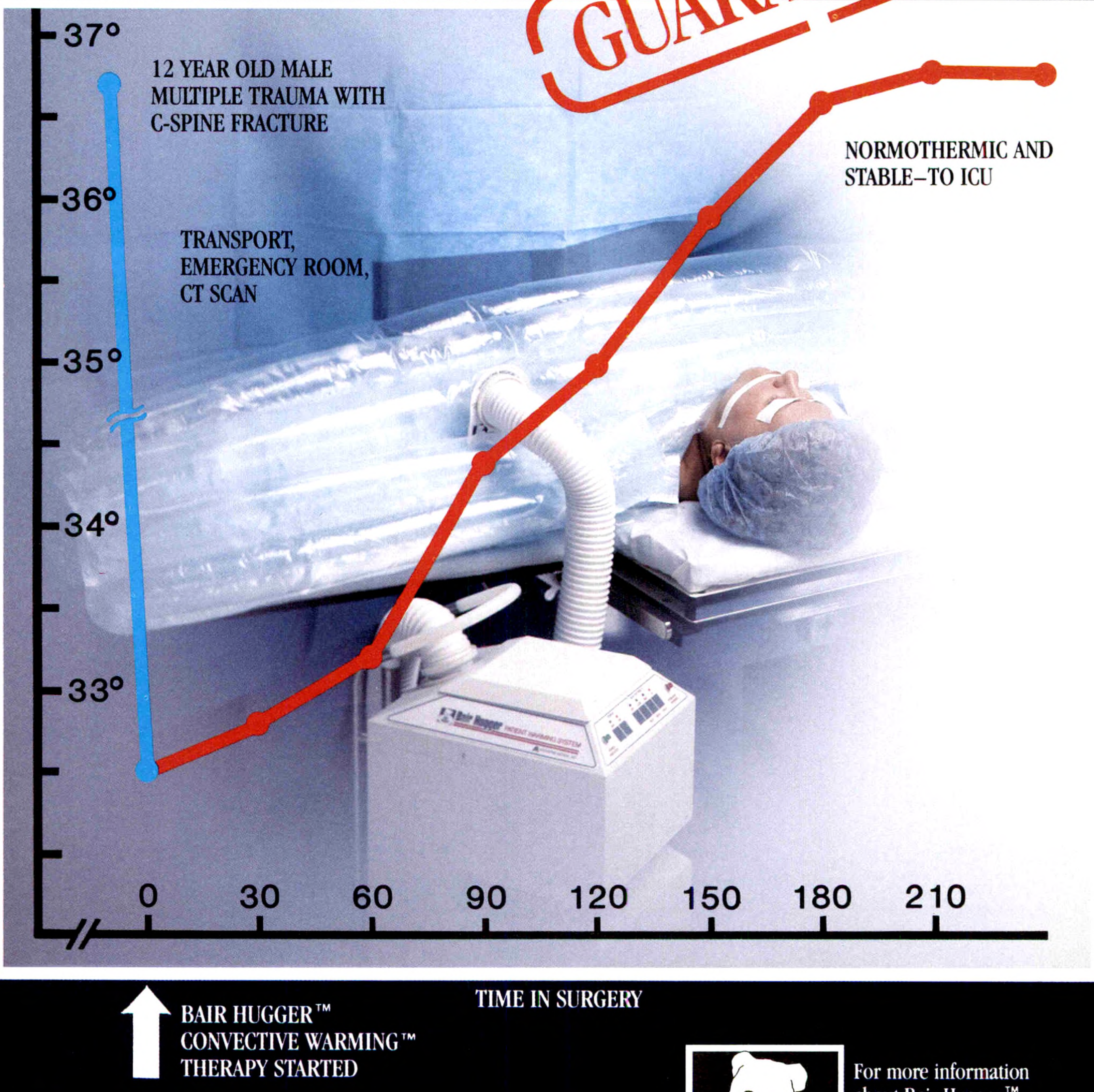
Volume 72, Number 2, February 1991

SCIENTIFIC ARTICLES

Prolongation of the QT Interval by Enflurane, Isoflurane, and Halothane in Humans	*William T. Schmeling, David C. Warltier, Donald J. McDonald, Karin E. Madsen, John L. Atlee, and John P. Kampine*	137
Pharmacokinetics and Pharmacodynamics of Doxacurium in Normal Patients and in Those With Hepatic or Renal Failure	*D. Ryan Cook, Judith A. Freeman, Allen A. Lai, Kerri A. Robertson, Yoogoo Kang, Richard L. Stiller, Sushma Aggarwal, Martha M. Abou-Donia, and Richard M. Welch*	145
Masseter Muscle Spasm in Children: Implications of Continuing the Triggering Anesthetic	*Judith A. Littleford, Leena R. Patel, Deepak Bose, Cal B. Cameron, and Cheryl McKillop*	151
Cerebral Blood Flow Decreases With Time Whereas Cerebral Oxygen Consumption Remains Stable During Hypothermic Cardiopulmonary Bypass in Humans	*Donald S. Prough, Anne T. Rogers, David A. Stump, Raymond C. Roy, A. Robert Cordell, Julia Phipps, and Carol L. Taylor*	161
Leukotriene Synthesis Inhibition and Receptor Blockade Do Not Inhibit Hypoxic Pulmonary Vasoconstriction in Sheep	*Ronald G. Pearl and Richard C. Prielipp*	169
Effects of Sufentanil on Cerebral Blood Flow, Cerebral Blood Flow Velocity, and Metabolism in Dogs	*Christian Werner, William E. Hoffman, Verna L. Baughman, Ronald F. Albrecht, and Jochen Schulte am Esch*	177
Respiratory Effects of Spinal Anesthesia: Resting Ventilation and Single-Breath CO_2 Response	*Richard A. Steinbrook and Mercedes Concepcion*	182
Saline-Filled Cuffs Help Prevent Laser-Induced Polyvinylchloride Endotracheal Tube Fires	*Mitchel B. Sosis and Francis X. Dillon*	187
Effect of Intraoperative Analgesic Therapy on End-Expired Concentrations of Halothane Associated With Spontaneous Eye Opening in Children	*Mehernoor F. Watcha, Richard G. Lagueruela, and Paul F. White*	190
Effects of Neuroleptic Agents on Rat Skeletal Muscle Contracture In Vitro	*Charlene A. Hon, Dennis F. Landers, and Anita A. Platts*	194
Clinical Responses to ORG 9426 During Isoflurane Anesthesia	*Timothy J. Quill, Maurice Begin, Peter S. A. Glass, Brian Ginsberg, and Michael S. Gorback*	203
Cardiorespiratory Effects of Antagonism of Diazepam Sedation With Flumazenil in Patients With Cardiac Disease	*Eran Geller, Pinchas Halpern, Joseph Chernilas, David Niv, and Hylton B. Miller*	207
Comparison of Percutaneous Losses of Sevoflurane and Isoflurane in Humans	*Stephen H. Lockhart, Nobuhiko Yasuda, Natalie Peterson, Michael Laster, Shahram Taheri, Richard B. Weiskopf, and Edmond I. Eger II*	212

NORMOTHERMIA IN THE O.R.

GUARANTEED*



*Terms of guarantee:

1. Bair Hugger™ Convective Warming Therapy must begin immediately after induction of anesthesia on the "high" setting and continue throughout the case if indicated.
2. Infused blood and fluids must be warmed to body temperature.

If these two criteria are met and the patient is hypothermic at the end of the operation (core temperature <36°C), Augustine Medical will replace the Warming Cover. This guarantee is limited to the replacement of the Warming Cover.

For more information about Bair Hugger™ Convective Warming Therapy, call 1-800-733-7775 or (612) 941-8866

AUGUSTINE MEDICAL INC.

Practical Solutions To Common Problems In Acute Care™

10393 West 70th Street • Eden Prairie, Minnesota 55344

SCIENTIFIC ARTICLES—*continued*

Hypokalemia Before Induction of Anesthesia and Prevention by β_2 Adrenoceptor Antagonism — *Evan D. Kharasch and T. Andrew Bowdle* — 216

Cardiovascular, Respiratory, and Analgesic Effects of Fentanyl in Unanesthetized Rhesus Monkeys — *Nancy A. Nussmeier, James L. Benthuysen, Eugene P. Steffey, John H. Anderson, Earl E. Carstens, John H. Eisele, Jr, and Theodore H. Stanley* — 221

Myocardial and Systemic Hemodynamics During Isovolemic Hemodilution Alone and Combined With Nitroprusside-Induced Controlled Hypotension — *George J. Crystal and M. Ramez Salem* — 227

CLINICAL REPORTS

Is Hypoxic Pulmonary Vasoconstriction Exaggerated During One-Lung Ventilation in Patients With Patent Ductus Arteriosus? — *Anis S. Baraka, Samar K. Taha, and Rania A. El-Khatib* — 238

A Supraclavicular Lateral Paravascular Approach for Brachial Plexus Regional Anesthesia — *S. S. Moorthy, Steven I. Schmidt, Stephen F. Dierdorf, Stephen H. Rosenfeld, and Jonathan M. Anagnostou* — 241

Nearly Fatal Cardiovascular Collapse During Total Hip Replacement: Probable Coronary Arterial Embolism — *William R. Camann, Gerald M. Sacks, Ann G. Schools, Steven T. Heggeness, Donald T. Reilly, and Mercedes Concepcion* — 245

Brainstem Toxicity With Reversible Locked-In Syndrome After Intrascalene Brachial Plexus Block — *Zia Durrani and Alon P. Winnie* — 249

Back Pain in Volunteers After Epidural Anesthesia With Chloroprocaine — *James M. Hynson, Daniel I. Sessler, and Beth Glosten* — 253

Spinal Anesthesia in a Patient With Friedreich's Ataxia — *Keshav Kubal, Shital K. Pasricha, and Mukul Bhargava* — 257

Myocardial Infarction Accompanying Acute Clonidine Withdrawal in a Patient Without a History of Ischemic Coronary Artery Disease — *Keith H. Berge and William L. Lanier* — 259

LETTERS TO THE EDITOR

Prevention of Nitrous Oxide-Induced Increases in Endotracheal Tube Cuff Pressure — *L. Brandt* — 262

Confirmation of Correct Endotracheal Tube Placement — *Ian Smith* — 263

Everything Old Is New Again — *Brian K. Bevacqua and William F. Cleary* — 263

Neurally Evoked Compound Electromyogram in the Clinical Setting — *Chingmuh Lee* — 264

In Response — *K. C. Huang* — 264

If You're Looking For The Best Anesthesiology Billing and Practice Management System, We've Got Your Number.

1-800-2GET-NHS

Call us today, and we'll send you a free information kit on the best computer system designed exclusively for anesthesiologists —The ULTRA Anesthesiology Billing and Practice Management System from Northern Health Systems.

You'll receive all of the information you need to automate your growing practice.

Information that will improve the efficiency of your office and speed your cash flow.

You'll discover a feature-packed system that can give you instant patient information. Simplify your accounting. Process your claims electronically. Produce customized reports. And much, much more.

Call us toll-free at 1-800-2GET-NHS for your free information kit. It's the only number you need.

NHS Northern Health Systems, Inc.
5500 Corporate Drive, Pittsburgh, PA 15237

LETTERS TO THE EDITOR—*continued*

Modification to an Anesthesia Breathing Circuit to Prolong Monitoring of Gases During the Use of Humidifiers	*Juraj Sprung and Eugene Y. Cheng*	264
Endobronchial Cuff Pressures of Double-Lumen Tubes	*Patrick T. Magee*	265
In Response	*David M. Gaba*	266
Reuse of a Disposable Stylet With Life-Threatening Complications	*Ritchard L. Fishman*	266
The Burden of Progress: A Fable	*J. S. Gravenstein*	267
Anesthesia Mortality in Perspective	*Robert D. Culling*	268
To the Editor	*John P. Abenstein*	269
Endotracheal Tube Cuff Failure Due to Valve Damage	*John E. Heusner and Christopher M. Viscomi*	270

BOOK REVIEWS

The Management of Pain, 2nd ed., by J. J. Bonica, J. D. Loeser, C. R. Chapman, and W. E. Fordyce, eds.	*Wilhelmina C. Korevaar*	271
Anesthesia for Cardiac Surgery by J. A. DiNardo and M. J. Schwartz, eds.	*Ellise S. Delphin*	271
Scientific Foundations of Anaesthesia. The Basis of Intensive Care by Cyril Scurr, Stanley Feldman, and Neil Soni, eds.	*Michael S. Gorback*	272
Gas Monitoring and Pulse Oximetry by J. S. Gravenstein	*Jeffrey B. Gross*	273
Perioperative Cardiac Dysrhythmias: Mechanisms, Recognition, Management, 2nd ed., by John Atlee III	*James R. Zaidan*	273
Books Received		274

THIC
5 mg/mL
10 mL
VERSED®
(midazolam HCl)
midazolam 5 mg/mL
(as the hydrochloride)
For I.M. or I.V. Use
disodium edetate, with 1% benzyl alcohol as
preservative and pH adjusted to approximately 3 with
hydrochloric acid and, if necessary, sodium hydroxide

Roche Laboratories
a division of Hoffmann-La Roche Inc.

Copyright © 1991 by Hoffmann-La Roche Inc. All rights reserved.

THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED_{50} of barbiturates or narcotics up to 75%.[1-4] This synergistic effect appears to result from a mutual enhancement of binding-site affinity.[1-3] Clinically, co-induction may decrease toxicity and speed recovery.[2] VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,[5] and its potent amnestic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- **Allows lower doses of induction agents[1-5]**
- **A smooth induction[5,6]**
- **Less risk of breakthrough awareness[5,6]**
- **A smooth emergence[5,6]**

Dosing considerations

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

Please see summary of product information on following page.

INJECTABLE
VERSED®
midazolam HCl/Roche Ⓘⓥ
FIRST

Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

References: 1. Tverskoy M, *et al.* Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. **2.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. **3.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. **4.** Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47. **5.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology.* 1982;57:279-284. **6.** Desiderio DP, Thorne AC. Awareness and general anaesthesia. *Acta Anaesthesiol Scand.* 1990;34(suppl 92):48-50.

VERSED®
(brand of midazolam HCl/Roche)Ⓒ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

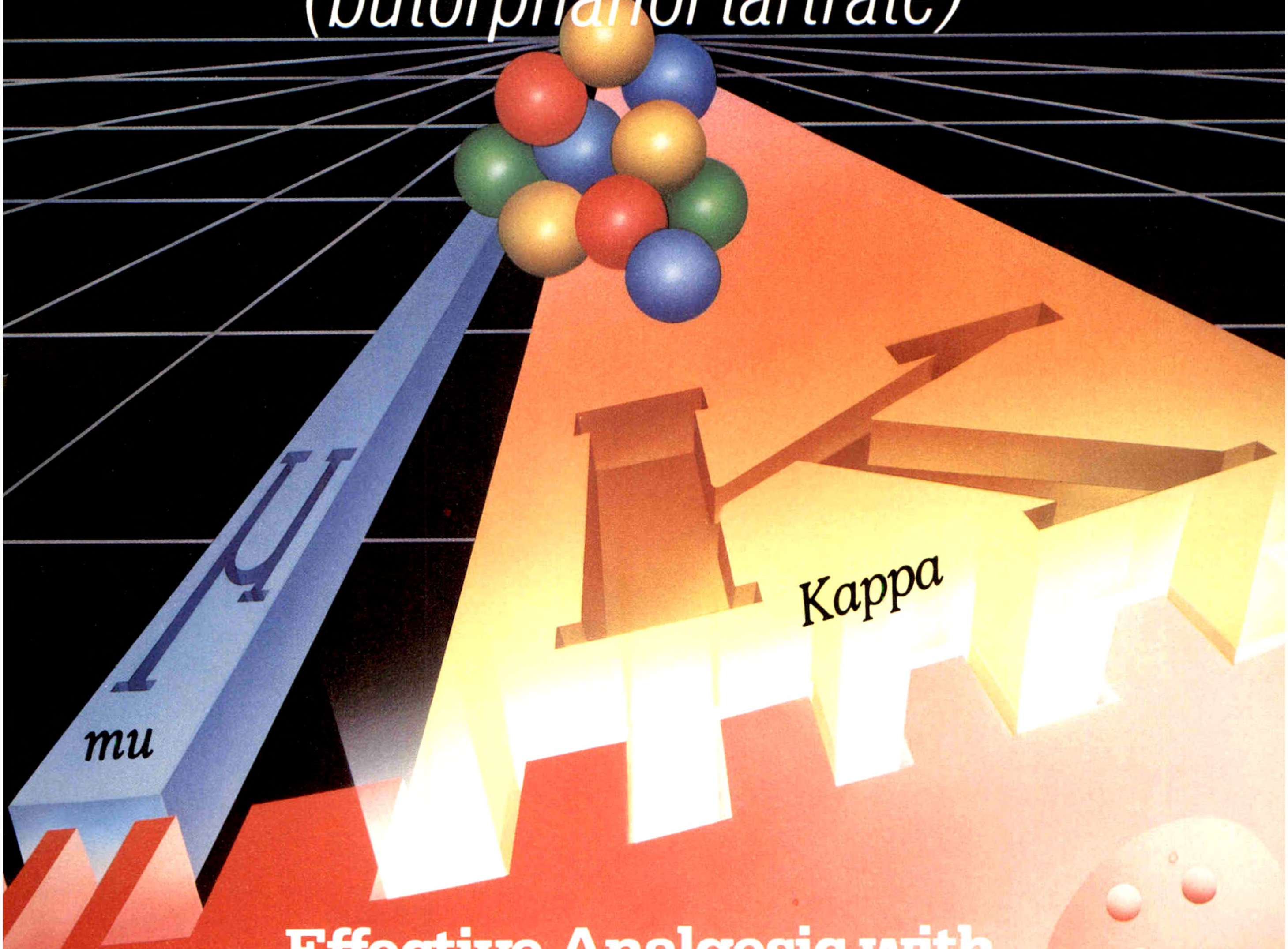
DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0988

Roche Laboratories
ROCHE®
a division of Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Stadol® IM IV

(butorphanol tartrate)



Effective Analgesic with Sedative Properties

- Premedicant for general anesthesia
- Adjunct to regional anesthesia
- For obstetrical analgesia
- Adjunct in ambulatory surgery

Anaquest

A BOC Health Care Company
Critical Care Worldwide

Artist's interpretation of Stadol molecule interacting with *kappa* and *mu* opioid receptors.

See brief summary of prescribing information on next page.

Stadol® is a Registered Trademark of Bristol-Myers Squibb Company

BRISTOL LABORATORIES
A Bristol-Myers Squibb Company
Evansville, Indiana 47721

Stadol® *(butorphanol tartrate)*

For complete information consult official package circular.

INDICATIONS AND USAGE
Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS
Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS
Patients Physically Dependent on Narcotics
Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Use During Balanced Anesthesia
Since the combined respiratory depressant effect of all intravenous medication used during conduct of general anesthesia may lead to underventilation or apnea, butorphanol should be administered during balanced anesthesia only by persons specifically trained in the use of intravenous anesthetics and adjuncts, the maintenance of a patent airway and management of respiratory effects of all intravenous medication administered.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Drug Dependence
Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure
Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects
Because Stadol increases the work of the heart, especially the pulmonary circuit, (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS
Certain Respiratory Conditions
Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function
Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery
Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Pre-operative or Pre-anesthetic Medication
Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Pregnancy
The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery
In general, the safety to the mother and fetus following the administration of Stadol during labor has been established; however, there have been a few reports of infant respiratory distress/apnea occurring after delivery (less than 1%; see Adverse Reactions). Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers
The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children
Safety and efficacy in children below age 18 years have not been established at present.

ADVERSE REACTIONS
The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (36, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations, seizures

Autonomic: flushing and warmth, dry mouth, sensitivity to cold

Cardiovascular: palpitation, increase or decrease of blood pressure

Gastrointestinal: Vomiting

Respiratory: slowing of respiration, shallow breathing, apnea

Dermatological: rash or hives

Eye: diplopia or blurred vision

OVERDOSAGE
Manifestations
Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment
The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

SUPPLY
Stadol (butorphanol tartrate Inj., USP) for I.M. or I.V. use is available as follows:
NDC 0015-5644-20 - 2 mg per mL, 2-mL vial
NDC 0015-5645-20 - 1 mg per mL, 1-mL vial
NDC 0015-5646-20 - 2 mg per mL, 1-mL vial
NDC 0015-5648-20 - 2 mg per mL, 10-mL multi-dose vial

For information on package sizes available, refer to the current price schedule.

BRISTOL LABORATORIES
Bristol-Myers
U.S. Pharmaceutical and Nutritional Group

IARS REVIEW COURSE LECTURES AVAILABLE

____ 1990, 64th Congress—26 Review Course Lectures—$10.00

____ 1989, 63rd Congress—27 Review Course Lectures—$10.00

____ 1988, 62nd Congress—26 Review Course Lectures—$10.00

____ 1987, 61st Congress—25 Review Course Lectures—$6.00

____ 1986, 60th Congress—26 Review Course Lectures—$6.00

____ 1985, 59th Congress—26 Review Course Lectures—$6.00

____ 1984, 58th Congress—24 Review Course Lectures—$6.00

____ 1983, 57th Congress—16 Review Course Lectures—$5.00

____ 1982, 56th Congress—14 Review Course Lectures—$5.00

To:
International Anesthesia Research Society
Suite 140, 2 Summit Park Drive
Cleveland, Ohio 44131-2553

Please send Lecture Booklets checked above.

My check, payable to IARS in the amount of $__________ is enclosed.

____
(Name)

____
(Mail Address)

____

____
(City, State, Zip)

The Osler Institute

Anesthesiology Review Course

§February 9-14, 1991 – Las Vegas

§April 15-20, 1991 – San Diego July 6-11, 1991 – Chicago

Now offering §60 hours of mock oral exams limited to 90 participants

OBJECTIVES

After this program attendees should:

- Have improved basic and clinical anesthesia knowledge
- Be better organized for further study of anesthesiology
- Be prepared to take written and oral exams

METHODS

- HOME STUDY MATERIALS consisting of a syllabus and assignments with questions and answers
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

§ Plus optional extra mock oral exam and video replay days February 15 and April 21-23, 1991

---

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

PHYSIOLOGY

- Respiratory Physiology
- Cardiovascular Physiology
- Neurophysiology
- Hepatic Physiology
- Renal Physiology
- Acid-Base and Blood Gas
- Endocrine Physiology
- Thermoregulation

PHARMACOLOGY

- Pharmacokinetics
- Inhalation Anesthetics
- Intravenous Anesthetics
- Muscle Relaxants
- Autonomic Drugs
- Central Nervous Drugs
- Cardiac & Diuretic Drugs
- Interactions & Genetics

PHYSICAL SCIENCES

- Applied Anatomy
- Physics and Gas Laws
- Anesthesia Machines
- Instrumentation
- Monitors and Ventilators
- Breathing Systems
- Defibrillators and Pacers

FUNDAMENTALS

- Preop. Evaluation & Prep.
- Patient Monitoring
- Airway Management
- Fluid and Blood Therapy
- Cardiopulmonary Disease
- Hepatic & Renal Disease
- Metabolic Disease
- Recovery Room

REGIONAL ANESTHESIA

- Local Anesthetics
- Autonomic Blocks
- Spinal and Epidural Blocks
- Caudal Blocks
- Upper Extremity Blocks
- Lower Extremity Blocks
- Chronic Pain Management

SPECIALTY AREAS

- Obstetric Anesthesia
- Pediatric Anesthesia
- Cardiac Anesthesia
- Thoracic Anesthesia
- Neuroanesthesia
- Ophthalmic & E.N.T.
- Geriatric and Outpatients
- Critical Care

FACULTY

Teresa Abboud, M.D.
Univ. of Southern California
Ezzat Abouleish, M.D.
U. of TX Med. Sch., Houston
Steven Barker, Ph.D., M.D.
University of California, Irvine
Jonathan Benumof, M.D.
Univ. of California, San Diego
T. A. Bowdle, M.D., Ph.D.
University of Washington
Floyd Brauer, M.D.
Loma Linda University
Burton Briggs, M.D.
Loma Linda University
Hernando DeSoto, M.D.
Riverside Hosp., Jacksonville
John Drummond, M.D.
Univ. of California, San Diego
Richard Engel, M.D.
Palomar Hosp., Escondido, CA
Christopher Gallagher, M.D.
Co-Author of *Board Stiff*
Carl Hess, M.D.
University of California, Irvine
Niels Jensen, M.D.
University of Iowa
George Khoury, M.D.
U. of California, Los Angeles
David Lubarsky, M.D.
Co-Author of *Board Stiff*
Terence Murphy, M.D.
University of Washington
Danae Powers, M.D.
Emory University
M. Nabil Rashad, M.D.
Baylor College of Medicine
Michael Ritter, M.D.
St. Louis University
Amira Safwat, M.D.
University of California, Davis
Joel Saltzman, M.D.
Las Vegas, Nevada
Mark Scheller, M.D.
Univ. of California, San Diego
Daniel Siker, M.D.
Medical College of Wisconsin
John Viljoen, M.D.
Univ. of Southern California
K.C. Wong, M.D.
University of Utah

*Accommodations were comfortable...."**

PROGRAM: This is more than a course – it is a whole program designed to prepare you for your board exams. Upon registration we will send you our home study material. At the course, one-on-one mock oral exams are held concurrent with most lectures and written question reviews. Each participant is assured a mock oral exam and observation of all non-private exams. A supplemental registration form will be sent on request to reserve mock oral sessions at any course and optional extra days of mock oral exams – April 21-23. Past participants recommend taking the course well before your exams and repeating for half price just before your exams.

*"...and those little extras...."**

LOWEST AIR FARES: Please call toll-free 1-800-548-8185 for group discounts.

*"...the most education for the money."**

FEES:

• 6 day lectures and mock orals:	$660
Residents and Fellows fee:	$440
Repeating course within 3 years:	$330
• Mock oral observation only (6 day):	$400
Per day mock oral observation:	$ 70
• Single examiner mock oral exam:	$ 70
• Dual examiner mock oral exam:	$140
• Surcharge for private exam:	$ 30
• Surcharge for videotaped exam:	$ 10
• Previous course syllabus:	$ 60

- **10% discount for fees paid more than two months before your course.**
- Attendees not in course hotel add $20/day.
- A deposit of $50 will reserve your position.
- Most home study materials will be mailed after half of the registration fee is received.

*"...home study material was extremely helpful."**

REFUNDS: Subject to $50 fee, refunds will be made up until the seminar begins.

*"I feel [the course] helped me pass ...."**

INFORMATION:

Joseph H. Selliken, Jr., M.D.
The Osler Institute
1094 Dawn Lane, P.O. Box 2218
Terre Haute, IN 47802
(800) 356-7537 or (812) 299-5658

* *Comments by past Osler participants*

Limited Enrollment: ANESTHESIOLOGY REVIEW COURSE REGISTRATION

Name ______________________________

Address ______________________________

City/State/Zip ______________________________

Phone ______________________________

Mail today to:

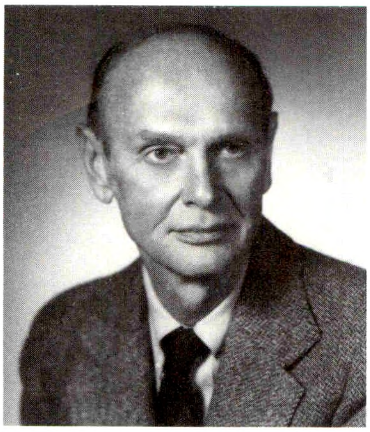
1094 Dawn Lane, Dept. A102
P.O. Box 2218
Terre Haute, IN 47802

For: ☐ February 9-14, 1991 – Las Vegas
☐ April 15-20, 1991 – San Diego
☐ July 6-11, 1991 – Chicago
☐ Check enclosed for $________
☐ Please send more information

IARS 65th CONGRESS
T.H. SELDON DISTINGUISHED LECTURE

"Anesthesia Journals: The Backbone of the Specialty — Past, Present, and Future"

Sunday, March 10, 1991—11:10 AM—Salon I
Marriott Rivercenter, San Antonio, Texas

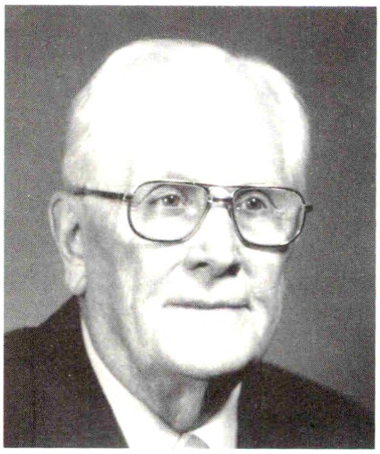


Nicholas M. Greene, MD

Professor Emeritus, Yale University
Department of Anesthesiology;
Editor, *ANESTHESIA AND ANALGESIA*

Dr. Greene's 41-year career in anesthesiology has included teaching posts at Harvard, the University of Rochester, and Chairmanship of the anesthesiology department at Yale. He has been editor in chief of both *ANESTHESIOLOGY* and *ANESTHESIA AND ANALGESIA* (retiring from the latter post in March 1991 after 14 years at the journal's helm). Though retired from clinical practice and journal editorship, Dr. Greene will continue to be active in the field of anesthesiology. His involvement with the ASA-sponsored Overseas Anesthesia Training Program, which will send its first volunteers to Lusaka, Zambia, in early 1991, promises to keep him busy. With its invitation to present the 1991 T.H. Seldon Distinguished Lecture, the IARS recognizes Dr. Greene's many and continuing contributions to our specialty.

The Lecture to be given by Dr. Greene is the ninth such to honor Dr. "Harry" Seldon, who served as Editor of *ANESTHESIA AND ANALGESIA* for 23 years ending in 1977.



T.H. Seldon, MD, FFARCS(I)

Rochester, Minnesota

ANESTH ANALG 1991;72:137–44

Prolongation of the QT Interval by Enflurane, Isoflurane, and Halothane in Humans

William T. Schmeling, MD, PhD, David C. Warltier, MD, PhD, Donald J. McDonald, MD, Karin E. Madsen, MD, John L. Atlee, MD, and John P. Kampine, MD, PhD

SCHMELING WT, WARLTIER DC, McDONALD DJ, MADSEN KE, ATLEE JL, KAMPINE JP. Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans. Anesth Analg 1991;72:137–44.

Previous investigations in laboratory animals have documented the ability of the volatile anesthetics to prolong the QT interval and the QT interval corrected for level of heart rate, QT_c. The purpose of the present investigation was to evaluate the direct electrocardiographic and hemodynamic effects of enflurane, isoflurane, and halothane in healthy, unpremedicated patients using an inhalation induction to avoid the confounding effects of other anesthetic agents. Experiments were conducted in 22 adult male patients, (ASA physical status I or II) divided into three groups given either enflurane ($n = 6$), isoflurane ($n = 8$), or halothane ($n = 8$) anesthesia. Twenty-four-hour preoperative, preinduction, and postinduction hemodynamic and electrocardiographic measurements were obtained. Anesthetic blood concentrations, levels of plasma electrolytes, and arterial blood gas tensions were also quantitated. Halothane administration (0.81 ± 0.06 mM) did not significantly alter the PR interval or QRS duration but significantly increased the QT (0.38 ± 0.01 to 0.45 ± 0.01 s) and QT_c intervals (0.39 ± 0.01 to 0.44 ± 0.02 s). Isoflurane anesthesia (1.04 ± 0.11 mM) did not significantly change QRS duration or PR and QT intervals but significantly prolonged the QT_c interval (0.42 ± 0.01 to 0.47 ± 0.14 s). Similarly, enflurane anesthesia (2.16 ± 0.13 mM) significantly prolonged the QT_c (0.40 ± 0.01 to 0.46 ± 0.14 s) without change in QRS duration or PR and QT intervals. Plasma electrolyte levels and arterial gas tensions remained within normal limits in all patients. All patients maintained a normal sinus rhythm during the study despite prolongation of the QT_c induced by the volatile anesthetics. These results extend previous observations in experimental animals to humans and suggest that ventricular repolarization is directly altered by the volatile anesthetics. Despite the absence of cardiac arrhythmias in this study, prolongation of the QT_c interval by volatile inhalation anesthetics suggests that caution should be used during administration of volatile anesthetics to patients with congenital, acquired, or pharmacologically induced prolongation of the QT_c.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane. HEART, ELECTROCARDIOGRAPHY—QT interval.

The QT interval, measured from the beginning of the QRS complex to the end of the T wave, represents the total duration of ventricular electrical systole including myocardial depolarization and repolarization (1–3). Previous evidence has implicated that a congenital or acquired prolongation of the QT interval may result in the development of reentrant ventricular arrhythmias including ventricular tachycardia, fibrillation, and asystole, resulting in syncopy and sudden cardiac death (4–7). An alteration or an asymmetric imbalance in normal sympathetic tone to the heart, or both, may partially underlie the prolongation of the QT interval (8–15). Anesthetic management of patients with congenital or acquired prolongation of the QT interval necessitates avoiding excess sympathetic discharge and pharmacologic agents that may augment the existing condition (16). Life-threatening arrhythmias and death during anesthesia have been reported in patients with prolongation of the QT interval (17–19).

Prolongation of the QT interval, corrected for changes in basal heart rate (QT_c), have been demonstrated in dogs with and without total autonomic nervous system blockade during enflurane, isoflu-

---

Supported in part by U.S. Public Health Service grants HL 36144, VA Medical Research Funds, and Anesthesiology Research Training Grant 1T32GM08377.

Received from the Departments of Anesthesiology and Pharmacology and Toxicology, The Medical College of Wisconsin and the Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin. Accepted for publication September 4, 1990.

Address correspondence to Dr. Schmeling, Medical College of Wisconsin, MFRC, Room A1000, 8701 West Watertown Plank Road, Milwaukee, WI 53226.

©1991 by the International Anesthesia Research Society

rane, and halothane anesthesia (20). Other canine studies have demonstrated prolongation of the QT interval after isoflurane anesthesia (21) and an increase in the duration of the cardiac action potential after administration of sufentanil or fentanyl (22).

Previous investigations have demonstrated prolongation of the QT_c interval in humans after thiopental and succinylcholine (23) as well as after sufentanil or fentanyl administration (24,25). A pediatric report has indicated that halothane and enflurane may prolong the QT_c interval in children (26). A recent study in humans also has demonstrated prolongation of the QT_c after induction with propofol and thiopental (27). However, no difference between the QT_c after induction and after 10 min of deep inhalation anesthesia with either enflurane or isoflurane and nitrous oxide in oxygen was observed (27). The authors speculated that only those drugs used for induction had any effect on the QT_c (27). The concomitant presence of multiple anesthetic and pharmacologic agents complicates interpretation of this (27) and other clinical investigations (23–26). The actions of the volatile anesthetics, halothane, isoflurane, and enflurane, on the QT interval when given alone have yet to be examined in humans (16). The purpose of the present investigation was to evaluate the electrocardiographic and hemodynamic effects of isoflurane, halothane, and enflurane in healthy, unpremedicated patients, using inhalation induction to avoid the effects of confounding agents.

Methods

Protocol

All protocols were approved by the Human Studies Subcommittees of the Medical College of Wisconsin and the Zablocki Veterans Administration Hospital. Twenty-two adult male patients, ASA physical status I or II, scheduled for elective surgical procedures were used in this study. None of the patients had a known history of cardiac disease. Additionally, none were receiving any medications known to affect the cardiovascular system. Specific exclusion criteria included abnormal serum electrolyte values (including potassium <3.5 or >5.5 mmol/L), previous history of hypertension, myocardial infarction, arrhythmia, heart failure, or angina, hepatic or renal disease, or malignancies. Cardiac medications that excluded patients from the study included slow channel calcium blocking agents, β-adrenergic antagonists, clonidine, potassium-wasting diuretics, and antiarrhythmic agents. Also, patients undergoing cardiopulmonary or neurosurgical procedures were excluded from this study.

Patients were randomly assigned to one of three groups for induction of anesthesia with either halothane, isoflurane, or enflurane. Preoperative evaluation included a presurgical electrocardiogram as well as recording of systemic arterial pressures and heart rate.

Preoperative sedation was withheld. Monitoring followed standard anesthetic practice and included measurement of systemic arterial pressure by direct radial artery recording or automated blood pressure cuffs, electrocardiogram, and pulse oximetry. All patients had preoperative fluid deficit replaced with normal saline solution and a preinduction electrocardiogram (leads I, II, III, AVR, AVL, AVF, and modified V_5) was recorded at 50 mm/s. Arterial pressure and heart rate were also recorded. The electrocardiogram (lead II or modified V) was continuously monitored for detection of arrhythmias or ischemia during the study.

Patients underwent slow inhalation induction of anesthesia, with a face mask, using either halothane, isoflurane, or enflurane in 100% oxygen. After induction of anesthesia, anesthesia was maintained with the same agent, and ventilation was assisted by face mask at 1.0–2.0 MAC inspired concentrations for 25–30 min. Excitement developed in four patients (one with enflurane, two with isoflurane, and one with halothane) during induction. Excitement was treated in one halothane and one isoflurane patient by addition of 70% nitrous oxide to the inspired gas for 30–45 s. One patient anesthetized with isoflurane and one patient anesthetized with enflurane in whom an excitement period developed were given 50 mg of thiopental. All four patients subsequently received only the volatile anesthetic. Twenty-five to thirty minutes after thiopental or nitrous oxide was given, there was no statistical difference between measured variables in all four patients and their group means for a similar time period. Therefore, these patients were included in the study.

After a 30-min equilibration period with the volatile anesthetic, an arterial blood sample was obtained for measurement of levels of serum electrolytes (including potassium, sodium, magnesium, and calcium), gas tensions, and gas chromatographic analysis of anesthetic blood concentrations using the method of Lowe (28). Recordings of the electrocardiogram and hemodynamic variables were again completed, and the experiment was terminated.

Table 1. Patient Data and Arterial Blood Chemistries After Halothane, Isoflurane, and Enflurane Anesthesia

	Halothane (n = 8)	Isoflurane (n = 8)	Enflurane (n = 6)
Age (yr)	52.8 ± 3.6	50.1 ± 4.9	46.2 ± 4.7
ASA physical status	1.5 ± 0.2	1.5 ± 0.2	1.3 ± 0.2
Weight (kg)	75.1 ± 2.8	85.9 ± 4.5	75.7 ± 3.9
pH	7.36 ± 0.03	7.35 ± 0.02	7.37 ± 0.03
$Paco_2$ (mm Hg)	38 ± 4	43 ± 3	42 ± 4
Pao_2 (mm Hg)	246 ± 12	283 ± 20	365 ± 22
HCO_3^- (mmol/L)	21 ± 1	23 ± 1	24 ± 1
Hct (%)	40 ± 1	40 ± 2	41 ± 1
Na^+ (mEq/L)	139 ± 1	139 ± 1	137 ± 2
K^+ (mEq/L)	4.1 ± 0.1	4.1 ± 0.2	3.9 ± 0.1
Ca^{2+} (mg/dL)	4.4 ± 0.1	4.6 ± 0.1	4.6 ± 0.1
Mg^{2+} (mg/dL)	1.9 ± 0.4	1.5 ± 0.1	1.5 ± 0.1

Analysis of Electrocardiographic Variables

Lead II and modified V_5 of the electrocardiogram were subsequently analyzed for RR interval, PR interval, QRS duration, and QT interval. The QT interval of longest duration during the preanesthetic control period was chosen, and the same lead was used for similar analysis after induction of anesthesia. The QT interval was corrected for heart rate by dividing the QT interval by the square root of the RR interval to obtain the QT_c interval (29). The average values of five independent determinations of the electrocardiographic variables from different cardiac cycles were used in this analysis.

Statistical Analysis

Data during the preoperative control, preanesthetic induction, and 30 min after anesthesia were compared using SAS software GLM followed by Bonferroni's modification of the *t*-test. An IBM AT clone microcomputer (Neat 286/20; Novas, San Jose, Calif.) interfaced with a Zoom modem (Zoom Telephonics, Mountain View, Calif.) to a VAX (Digital Electronic Corp., Cambridge, Mass.) mainframe computer was used for statistical calculations. Differences between conscious and anesthetized states were considered significant when the probability (P) value was <0.05. All data are expressed as mean ± SEM.

Results

Patient Demographics

The mean ages, ASA physical status, and patient weights in the halothane, isoflurane, and enflurane groups are listed in Table 1. There were no significant differences between the groups. Preoperative electrocardiograms before anesthesia showed normal values for the PR, QT, and QT_c intervals, as well as for the QRS duration. All baseline measurements of hemodynamic variables (systolic and diastolic systemic arterial pressures and heart rate) were within normal limits and not significantly different among the groups.

Hemodynamic and Electrocardiographic Effects of Halothane

Preanesthetic induction levels of systemic arterial pressures and heart rate were not significantly different from the 24-h preoperative values (Figure 1). Halothane anesthesia was associated with statistically significant decreases in systolic and diastolic arterial pressures without altering heart rate (Figure 1). Arterial blood gas tension values and serum electrolyte concentrations were all within normal limits after halothane induction (Table 1). At the time of electrocardiographic analysis after anesthetic induction, the halothane concentration in arterial blood was 0.81 ± 0.06 mM. Halothane produced no change in PR interval or in QRS duration (Figure 2). However, halothane significantly prolonged the QT and QT_c intervals (from 0.38 ± 0.01 to 0.45 ± 0.01 s and from 0.39 ± 0.01 to 0.44 ± 0.02 s, respectively). Typical effects of halothane on the electrocardiogram are demonstrated in Figure 3.

Hemodynamic and Electrocardiographic Effects of Isoflurane

The preoperative levels of systemic arterial pressure and heart rate were not significantly different from

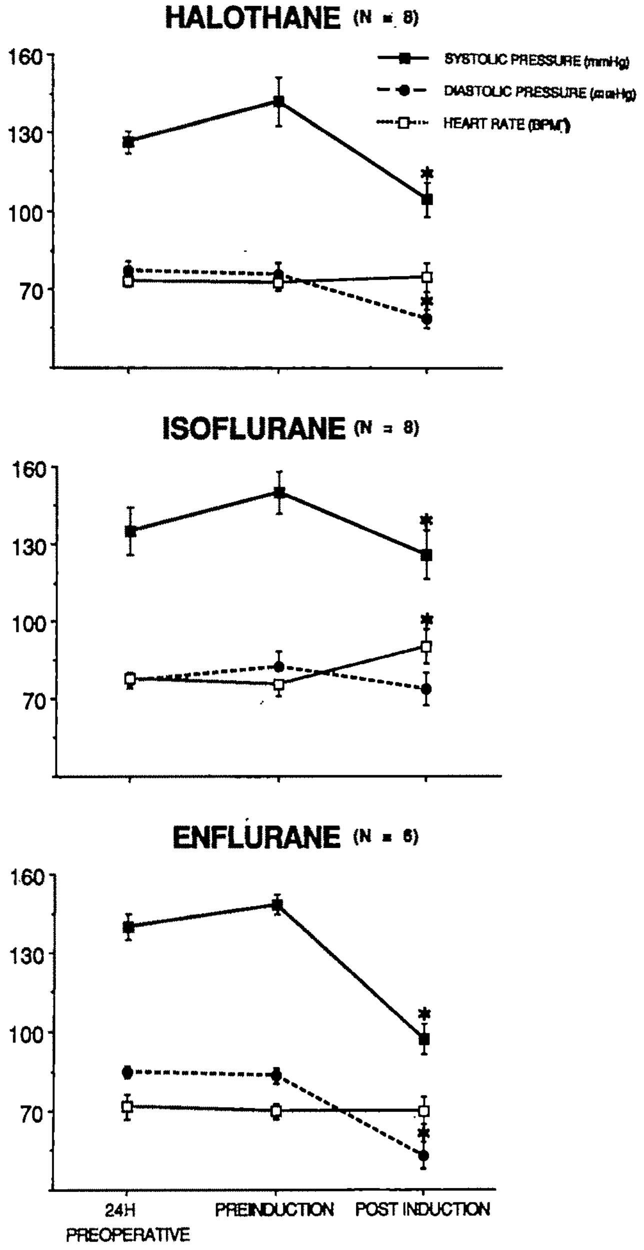


Figure 1. Twenty-four-hour preoperative, immediate preinduction, and postanesthetic induction values for diastolic and systolic arterial pressures and heart rate. Mean ± SEM data. *Significantly ($P < 0.05$) different from preinduction control values.

those obtained in the operating room in patients anesthetized with isoflurane (Figure 1). Administration of isoflurane decreased systemic arterial pressure (Figure 1) and produced a statistically significant increase in heart rate (from 75 ± 5 to 90 ± 7 beats/min). Blood chemistries after anesthetic induction were similar to those seen in the halothane group, and all values were within normal limits (Table 1). At the time electrocardiograms were recorded after anesthetic induction, the isoflurane arterial blood concentration was 1.04 ± 0.11 mM.

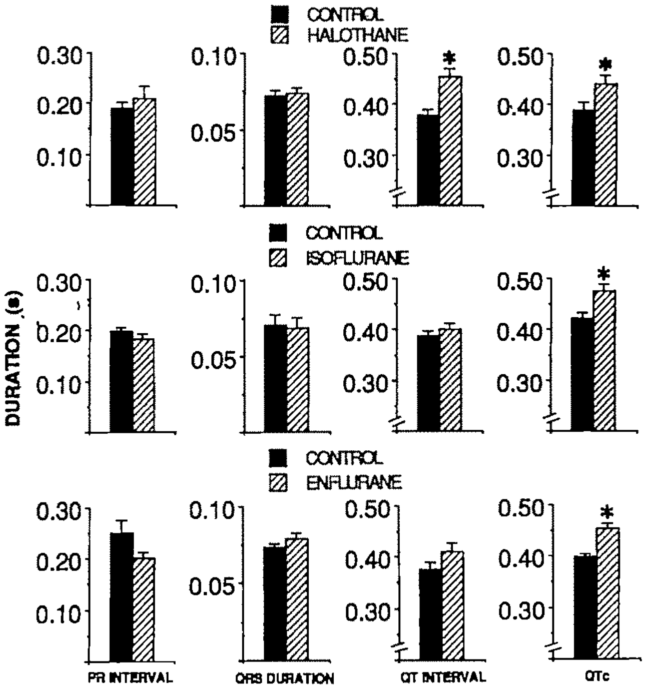


Figure 2. Changes in length of PR interval, QRS duration, QT interval, and QT_c produced by halothane ($n = 8$), isoflurane ($n = 8$), and enflurane ($n = 6$). Mean ± SEM data. *Significantly different from preinduction control values.

Isoflurane administration resulted in no significant change in the PR interval, QRS duration, and QT interval. However, the QT_c was significantly prolonged (from 0.42 ± 0.01 to 0.47 ± 0.01 s) during isoflurane anesthesia (Figure 2). Typical effects of isoflurane on the electrocardiogram are demonstrated in Figure 3.

Hemodynamic and Electrocardiographic Effects of Enflurane

The preoperative and baseline hemodynamic and electrocardiographic values for the enflurane group are summarized in Figures 1 and 2. After anesthetic induction with enflurane, there was a statistically significant decrease in both systolic and diastolic arterial pressures without a change in heart rate (Figure 1). Arterial blood gas tensions and levels of serum electrolytes during enflurane are shown in Table 1. The arterial blood concentration of enflurane during electrocardiographic sampling was 2.16 ± 0.13 mM. Similar to isoflurane, enflurane did not alter the PR interval, QRS duration, and the QT interval. However, QT_c was significantly prolonged during enflurane anesthesia (from 0.40 ± 0.01 to 0.46 ± 0.01 s) (Figure 2). Typical actions of isoflurane on the electrocardiogram are illustrated in Figure 3.

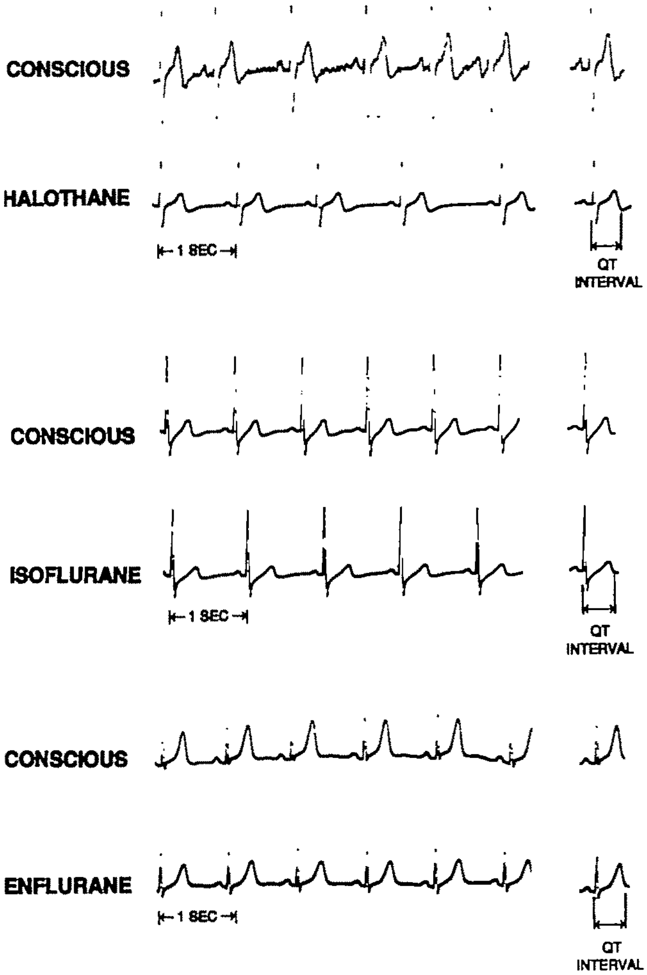


Figure 3. Typical strip chart electrocardiogram from three healthy male patients before and after anesthetic induction with halothane, isoflurane, and enflurane. Note the prolongation of the QT interval after halothane without change in the PR interval or QRS duration.

Discussion

The QT interval extends from the beginning of the QRS complex to the end of the T wave. This portion of the electrocardiogram represents both electrical depolarization and repolarization of the ventricles (1). There exist at least two congenital long QT syndromes. The first, the Jervell–Lange-Nielsen syndrome (30), is associated with congenital deafness, syncopal attacks, and sudden death secondary to ventricular fibrillation. The second, as described by Romano et al. (31) and Ward (32) is similar to the Jervell–Lange-Nielsen syndrome, but occurs more frequently and is not associated with neural deafness (8,9). Pharmacologic management of patients with congenital or acquired prolonged QT interval syndromes frequently includes β-adrenergic blockade to shorten the QT interval and the QT_c (8). Patients who have responded to β-adrenergic blockade are usually more successfully managed during anesthesia than those patients refractory to such treatment (10,16).

An asymmetric imbalance in the activities of the right- versus left-sided sympathetic nerves innervating the heart has been postulated to be a mechanism for prolongation of the QT interval (8,10–15). A reduction in the right cardiac nerve or an increase in left cardiac nerve sympathetic activity, or both, may result in prolongation of the QT interval, lower the threshold for ventricular fibrillation, and augment ventricular excitability. While the sympathetic imbalance in cases of prolonged QT interval cannot always be well defined (8,11,14,15), therapeutic interventions in cases of both congenital and acquired prolonged QT interval have included left stellate ganglion block and surgical ganglionectomy. Such procedures have been shown to shorten the QT interval and to raise the fibrillation threshold by abolishing asymmetric cardiac sympathetic innervation.

Multiple causes of acquired prolonged QT interval exist. Many drugs including agents that interfere with the autonomic nervous system and antiarrhythmic agents are known to lengthen the QT_c. Disturbances in normal myocardial function, thermal and electrolyte alterations, neurological, endocrine, and metabolic disturbances, and multiple pharmacologic agents have all been reported to prolong the QT interval (10,16). In the present investigation, no patient had preexisting evidence of myocardial disease, serum electrolyte abnormalities, and endocrine or metabolic disturbances, and all remained normothermic. Patients with neurologic dysfunction were specifically excluded.

In a recent investigation from this laboratory, prolongation of the QT interval was demonstrated after autonomic nervous system blockade in dogs anesthetized with halothane, enflurane, or isoflurane (20). Therefore, prolongation of the QT interval may be a direct myocardial effect of the volatile anesthetics independent of change in autonomic nervous system tone. Results of the present study are in agreement with this previous investigation (20). Furthermore, no alterations were found in the QRS intervals of patients after volatile anesthetic induction in this study. This implies that the prolongation of the QT interval reflects delayed repolarization, possibly independent of autonomic constraints.

Previous evidence has implicated a prolongation of the QT_c in the development of reentrant ventricular arrhythmias resulting in syncopy and sudden cardiac death (4–7). This is believed to be due to an increase in the ventricular vulnerable period (relative refractory period) of the heart to arrhythmogenic potential, as well as an increase in the incidence of premature ventricular beats (8,16,33,34). However, more recent evidence indicates that not all QT interval prolongation is necessarily arrhythmogenic (35,36). Previous reports have documented the ability of various anesthetic agents including succinylcholine to alter the QT interval (10,16,23). Prolongation of the QT interval induced by succinylcholine may be secondary to its ability to stimulate simultaneously parasympathetic and sympathetic ganglia with a resultant imbalanced cardiac innervation (23). Whereas prior administration of *d*-tubocurarine blocked this effect of succinylcholine, pancuronium (23) did not. The latter agent has also been associated with the induction of ventricular fibrillation in a patient with prolonged QT syndrome (37).

Induction of anesthesia with thiopental may (23) or may not (38) prolong the QT interval. McConachie et al. (27) reported that thiopental or propofol used for induction both significantly prolonged the QT_c, and the effect of thiopental was greater than propofol. Subsequent maintenance anesthesia with either enflurane or isoflurane and nitrous oxide did not result in further increases in QT_c. However, patients received temazepam as a premedicant in this study, and concentrations of the volatile anesthetics were not measured making comparison with the present results difficult. Few studies specifically address the effect of volatile anesthetics on the QT interval. During electrophysiologic studies in a pediatric patient with congenitally prolonged QT, Hartzler and Osborn (14) reported a decrease in the QT interval associated with episodic ventricular fibrillation upon anesthetic emergence and subsequent ventricular fibrillation upon reinduction of anesthesia 48 h later. Other studies in patients with prolonged QT interval have demonstrated that isoflurane produced a beneficial action on the QT interval (17,39). Studies conducted on experimental animals have shown a prolongation of the QT interval with halothane, enflurane, and isoflurane in chronically instrumented dogs (20) as well as a prolongation by all three agents in dogs with recent myocardial infarction (40). In a study of 100 patients anesthetized with isoflurane or sufentanil, Roizen et al. (24) reported a prolongation of the QT_c with both agents. The authors concluded that prolongation of the QT_c interval may not be a valid reason to choose between narcotic and inhalation anesthesia. In this study, additional anesthetic agents were used for premedication, induction, and maintenance and may have contributed to the observed results. In the present study, only inhalation anesthesia without premedication was used, but the present results support the previous observations in humans that halothane, enflurane, and isoflurane prolong the QT_c.

In the present study, no significant alterations in the PR interval or QRS duration were observed. Hence, the prolongation of the QT_c reflected delayed repolarization. A previous study has discussed in length the apparent discrepancy between the increase in repolarization produced by the volatile anesthetics in the intact heart and an apparent decrease in total action potential duration demonstrated in vitro (20). That study concluded that altered bioavailability or concentration gradients of ionic species, disruption of the electrical syncytium of the heart, or dissociation of electrical-mechanical coupling of the heart may underline reported differences between the effects of volatile anesthetics in vivo and in vitro (20). Other in vitro investigations have speculated that a decrease in the slow calcium channel current, possibly in combination with subsequent alterations in potassium and sodium currents, contributes to a decrease in the action potential duration with varying effects on the plateau and repolarization phases (41–43). Alterations in a diversity of channel currents, including calcium (44), sodium (45), and potassium (46), may contribute to the production of early afterdepolarizations and prolongation of repolarization with possible arrhythmogenicity. It is possible that volatile anesthetic-induced alterations in calcium and potassium channel currents may underlie the repolarization abnormalities observed in the present study. However, paradoxically, despite these repolarization abnormalities no overt arrhythmias were observed in this study or are apparent in general anesthetic practice.

Early studies demonstrated a relationship between pharmacologically induced prolongation of the QT interval and the resultant paroxysmal ventricular arrhythmia of torsades de pointes (2,3,6,8,36). However, there is no linear relationship between QT interval prolongation and the development of torsades de pointes (36). Additionally, certain antiarrhythmic agents, including those of classes Ia and III, prolong repolarization as a partial mechanism of action. Evidence indicates that the lengthening of the QT interval by agents such as amiodarone and sotalol actually contributes to antiarrhythmic and antifibrillatory actions (35,36). The development of torsades de pointes or of other ventricular arrhythmias may require a combination of two or more agents that prolong the QT interval, the concomitant presence of electrolyte abnormalities (e.g., low potassium or magnesium), or existent endocrine dysfunction (e.g., hyperthyroidism) (35,36,45). None of the patients in the present investigation had concomitant therapy with other drugs that lengthen the QT interval, electrolyte disturbances, or endocrine abnormalities.

The precise mechanism whereby ionic channels are affected by agents that prolong the QT interval with resulting antiarrhythmic or arrhythmogenic potential is unknown. Certain agents such as bepridil, a calcium channel antagonist, significantly prolong the QT interval and have been reported to induce torsades de pointes but usually only with concomitant electrolyte abnormalities (47). The reported ability of volatile anesthetics to alter channel conductance for several ionic species may underlie the prolongation of the QT interval without overt arrhythmogenic action (10,41–43). Additionally, the documented propensity for cardiac arrhythmias during volatile anesthesia in the presence of high catecholamines or hypokalemia may be a consequence of actions on different ionic channels interacting with the effects of the anesthetics.

Therefore, although volatile anesthetics prolong the QT interval, as demonstrated in the present study, such an action may resemble the class III antiarrhythmic agents that also prolong the QT interval. However, when administered in the presence of other agents or of conditions that prolong the QT interval, volatile anesthetics may be arrhythmogenic by augmenting such QT prolongation. Further studies concerning the specific effects of the volatile agents on various ionic channel currents are required to define precisely such conditions. Whether a prolongation of the QT interval is a general consequence of anesthetic induction as demonstrated in numerous previous reports (20,21,23,27) using a variety of anesthetic agents (10,16,21–26) remains to be determined. Whether such changes after anesthesia in humans reflect alterations in endogenous autonomic tone will require additional investigations.

The authors acknowledge Mimi Mick and David Schwabe for excellent assistance in the completion of this manuscript.

References

1. Atlee JL, ed. Normal electrical activity of the heart. In: Perioperative cardiac dysrhythmias, 2nd ed. Chicago: Year Book Medical Publishers, 1990:14–56.
2. Surawicz B, Knoebel SB. Long QT: good, bad or indifferent. J Am Coll Cardiol 1984;4:398–413.
3. Moss HJ. Prolonged QT-interval syndromes. JAMA 1986;256: 2985–7.
4. Surawicz B. The QT interval and cardiac arrhythmias. Annu Rev Med 1987;38:81–90.
5. Nikolic G, Bishop RL, Singh JB. Sudden death recorded during halter monitoring. Circulation 1982;66:218–25.
6. Han J, Goel BG. Electrophysiologic precursors of ventricular tachyarrhythmias. Arch Intern Med 1972;129:749–55.
7. Schwartz PJ, Wolfe. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074–7.
8. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. Am Heart J 1975;89:378–90.
9. Garza LA, Vick RL, Nora JJ, McNamara DG. Heritable QT prolongation without deafness. Circulation 1970;41:39–48.
10. Atlee JL. Causes for perioperative dysrhythmias. In: Perioperative cardiac dysrhythmias. 2nd ed. Chicago: Year Book Medical Publishers, 1990:187–273.
11. Cinca J, Evangelista A, Montoyo J, et al. Electrophysiologic effects of unilateral right and left stellate ganglion block on the human heart. Am Heart J 1985;109:46–54.
12. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. N Engl J Med 1971;285:903–4.
13. Yanowitz BA, Preston JB, Abildskov JA. Functional distribution of right and left stellate innervation to the ventricles: production of neurogenic electrocardiograph changes by unilateral alteration of sympathetic tone. Circ Res 1966;18:416–28.
14. Hartzler GO, Osborn MJ. Invasive electrophysiological study in the Jervell and Lange Nielsen Syndrome. Br Heart J 1981; 45:225–9.
15. Milne JR, Ward DE, Spurrell RA, Camm AJ. The long QT syndrome; effects of drugs and left stellate ganglion block. Am Heart J 1982;104:194–8.
16. Galloway PA, Glass PS. Anesthetic implications of prolonged QT interval syndromes. Anesth Analg 1985;64:612–20.
17. Medak R, Benumof JL. Perioperative management of the prolonged QT interval syndrome. Br J Anaesth 1983;55:361–4.
18. Forbes RB, Morton GH. Ventricular fibrillation in a patient with unsuspected mitral valve prolapse and a prolonged QT interval. Can Anaesth Soc J 1979;26:424–7.
19. Wig J, Bali IM, Singn RG, Kataria RN, Khattri HN. Prolonged QT interval syndrome. Sudden cardiac arrest during anaesthesia. Anaesthesia 1979;34:37–40.
20. Riley DC, Schmeling WT, Al-Wathiqui MH, Kampine JP, Warltier DC. Prolongation of the QT interval by volatile anesthetics in chronically instrumented dogs. Anesth Analg 1988;67:741–9.
21. Riley DC, Gross GJ, Kampine JP, Warltier DC. Specific bradycardia agents, a new therapeutic modality for anesthesiology: hemodynamic effects of UL-FS 49 and propranolol in conscious and isoflurane-anesthetized dogs. Anesthesiology 1987;67: 707–16.
22. Blair JR, Pruett JK, Adams RJ, Crumine RS. The electrophysiologic effects of opiates in canine Purkinje fibers. Anesthesiology 1986;65:A406.
23. Saarnivaara L, Lindgren L. Prolongation of the QT interval during induction of anaesthesia. Acta Anaesthesiol Scand 1983;27:126–30.
24. Roizen MF, Lampe GH, Benefiel DJ, et al. Change in QT interval with anesthesia: should it determine whether to use a narcotic or inhalational agent? Anesthesiology 1988;69:A53.
25. Blair JR, Pruett JK, Crumrine RS, Balser SS. Prolongation of the QT interval in association with the administration of large doses of opiates. Anesthesiology 1987;67:442–3.
26. Lindgren L. E.C.G. changes during halothane and enflurane anaesthesia for E.N.T. surgery in children. Br J Anaesth 1981;53:653–62.
27. McConachie I, Keaveny JP, Healy TE, Vohra S, Million L. Effect of anaesthesia on the QT interval. Br J Anaesth 1989;63: 558–60.

28. Lowe HJ. Flame ionization detection of volatile organic anesthetics in blood, gases and tissues. Anesthesiology 1964;25: 808–14.
29. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353–70.
30. Jervell A, Lange-Nielsen F. Congenital deaf mutism, functional heart disease with prolongation of the QT interval and sudden death. Am Heart J 1957;54:59–68.
31. Romano C, Gemme G, Pongiglione R. Artimie cardiache rare deletapediatrica. Clin Pediatr (Bologna) 1963;45:656–83.
32. Ward OC. New familial cardiac syndrome in children. J Ir Med Assoc 1964;54:103–106.
33. Abildskov JA. The prolonged QT interval. Annu Rev Med 1979;30:171–9.
34. Kenny RA, Sutton R. The prolonged QT interval—a frequently unrecognized abnormality. Postgrad Med J 1985;61:379–86.
35. Singh BN, ed. Control of cardiac arrhythmias by lengthening repolarization. Mount Kisco, NY: Futura Publishing, 1988:1–577.
36. Singh BN. When is QT prolongation antiarrhythmic and when is it proarrhythmic? Am J Cardiol 1989;63:867–9.
37. Ponte J, Lund J. Prolongation of the QT interval (Romano–Ward syndrome): anaesthetic management. Br J Anaesth 1981; 53:1347–50.
38. Wilton NC, Hantler CB. Congenital long QT syndrome: changes in QT interval during anesthesia with thiopental, vecuronium, fentanyl and isoflurane. Anesth Analg 1987;66: 357–60.
39. Carlock FJ, Brown M, Brown EM. Isoflurane anesthesia for a patient with long QT syndrome. Can Anaesth Soc J 1984;31: 83–5.
40. Deutsch N, Hantler CB, Tait AR. AT interval lengthening with halothane, enflurane and isoflurane in dogs with recent myocardial infarction. Proceedings of the 11th Annual Meeting of the Society of Cardiovascular Anesthesiologists, Seattle, Wash.: 1989:221.
41. Turner LA, Bosnjak ZJ, Kampine JP. Actions of halothane on the electrical activity of Purkinje fibers derived from normal and infarcted canine hearts. Anesthesiology 1987;67:619–29.
42. Hirota K, Ito Y, Masuda A, Momose Y. Effects of halothane on membrane ionic currents in guinea pig atrial and ventricular myocytes. Acta Anaesthesiol Scand 1989;33:239–44.
43. Ikemoto Y, Yatani A, Arimura H, Yoshitake J. Reduction of the slow inward current of isolated rat ventricular cells by thiamylal and halothane. Acta Anaesthesiol Scand 1985:29:583–6.
44. Tanaka C, Singh BN. Barium-induced non-driven action potentials as a model of triggered potentials from early afterdepolarizations: significance of slow channel activity and differing effects of quinidine and amiodarone. J Am Coll Cardiol 1990;15:213–21.
45. Zipes DP. Cardiac electrophysiology: promises and contributions. J Am Coll Cardiol 1989;13:1329–52.
46. Roden DM, Woosley RL, Primm PK. Incidence and clinical features of the guinidine-associated long QT syndrome: implications for patient care. Am Heart J 1986;111:1088–96.
47. Manouvrier J, Sagot M, Carson C, et al. Nine cases of torsades depointes with bepridil administration. Am Heart J 1986;111: 1005–7.

ANESTH ANALG
1991;72:145–50

LIBRARY

Pharmacokinetics and Pharmacodynamics of Doxacurium in Normal Patients and in Those With Hepatic or Renal Failure

D. Ryan Cook, MD, Judith A. Freeman, MBChB, Allen A. Lai, PhD, Kerri A. Robertson, MD, Yoogoo Kang, MD, Richard L. Stiller, PhD, Sushma Aggarwal, MD, Martha M. Abou-Donia, PhD, and Richard M. Welch, PhD

COOK DR, FREEMAN JA, LAI AA, ROBERTSON KA, KANG Y, STILLER RL, AGGARWAL S, ABOU-DONIA MM, WELCH RM. Pharmacokinetics and pharmacodynamics of doxacurium in normal patients and in those with hepatic or renal failure. Anesth Analg 1991; 72:145–50.

We determined the pharmacokinetics and duration of action of a bolus dose of doxacurium (15 $\mu g/kg$) in 27 patients anesthetized with isoflurane and nitrous oxide. Nine patients had normal renal and liver functions and were undergoing a variety of surgical procedures, nine were undergoing cadaveric kidney transplantation because of end-stage renal disease, and nine were undergoing cadaveric liver transplantation because of end-stage hepatocellular disease. Plasma concentrations of doxacurium were measured for 6 h after administration using a sensitive and specific capillary gas chromatographic assay. Plasma concentration versus time data were analyzed by a noncompartmental method based on statistical moments. Neuromuscular blockade was assessed by measuring the electromyographic evoked response of the adductor pollicis muscle to train-of-four stimulation of the ulnar nerve. The degree of neuromuscular blockade after doxacurium administration was described as the percent of control of the first train-of-four response. The pharmacokinetic variables were (normal vs hepatic failure vs renal failure, respectively): volume of distribution at steady state (220 ± 110 vs 290 ± 60 vs 270 ± 130 mL/kg [mean ± SD]), plasma clearance (2.7 ± 1.6 vs 2.3 ± 0.4 vs 1.2 ± 0.7 $mL \cdot kg^{-1} \cdot min^{-1}$), mean residence time (95.2 ± 57 vs 129.4 ± 30 vs 270 ± 210 min), and elimination half-life (99 ± 54 vs 115 ± 31 vs 221 ± 156 min). Plasma clearance and mean residence time differed significantly between patients with renal failure and control patients. There was no significant difference in the onset times or in clinical effective duration, although the clinical duration tended to be longer and more variable in the patients with renal failure. This unpredictable response and the possibility of prolonged blockade should be borne in mind if doxacurium is to be used in patients with renal failure.

Key Words: NEUROMUSCULAR RELAXANTS, DOXACURIUM. PHARMACOKINETICS, DOXACURIUM. KIDNEY, RENAL FAILURE—doxacurium. LIVER, HEPATIC FAILURE—doxacurium.

Doxacurium, a potent benzylisoquinolinium nondepolarizing neuromuscular blocking agent, has a long duration of action and is devoid of cardiovascular and histamine-releasing side effects at clinically effective doses (1,2). Although initial animal studies suggest that doxacurium is primarily excreted in unchanged form by the kidney, the relative roles of the liver and kidney in the elimination of doxacurium in humans have not yet been determined. This study was designed to evaluate the pharmacokinetics of doxacurium in adults with normal kidney and liver functions and in adults with either kidney or liver failure.

Methods

Twenty-seven surgical patients, 19–55 yr of age, were studied in three groups. The study was approved by the hospital's Institutional Review Board, and informed written consent was obtained from each patient. Nine patients (ASA physical status III and IV) had end-stage liver disease (primary biliary cirrhosis,

---

Received from the Departments of Anesthesiology, Presbyterian-University Hospital and the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania and Burroughs Wellcome Co., Research Triangle Park, North Carolina. Accepted for publication September 4, 1990.

Address correspondence to Dr. Cook, Department of Anesthesiology, Children's Hospital of Pittsburgh, One Children's Place, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213-2583.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Demographic Information and Screening Clinical Laboratory Data

	Control	Patients	
	(*n* = 9)	With hepatic failure (*n* = 7)	With renal failure (*n* = 8)
Age (yr)	32.1 ± 7.3	43.0 ± 11.2	38.7 ± 8.0
Weight (kg)	82.2 ± 11.6	62.8 ± 9.4	72.9 ± 11.1
Hematocrit (%)	36.3 ± 5.7	35.4 ± 4.4	25.4 ± 5.6[a]
BUN (mg/dL)	13.6 ± 3.7	11.4 ± 7.9	60.3 ± 24.8[a]
Creatinine (mg/dL)	0.9 ± 0.1	0.8 ± 0.4	9.6 ± 2.9[a]
Alkphos (IU/L)	55.1 ± 15.4	347 ± 402[a]	88.5 ± 25.2
AST (IU/L)	27.1 ± 22.8	225 ± 288[a]	20.7 ± 25.4
ALT (IU/L)	19.5 ± 8.5	61 ± 41	22.4 ± 11.5
Bilirubin (mg/dL)	0.7 ± 0.5	15.4 ± 16.1[a]	0.5 ± 0.1
Albumin (g/dL)	3.9 ± 0.4	2.6 ± 0.6	3.9 ± 0.4
GGTP (IU/L)	19.6 ± 10.2	276 ± 525[a]	34.8 ± 21.1

Alkphos, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGTP, γ-glutamyl transpeptidase.
Values are mean ± SD.
[a] Significant differences (analysis of variance) from control patients.

postnecrotic cirrhosis, and chronic active hepatitis) and were to undergo cadaveric hepatic transplantation; nine patients (ASA physical status III) had end-stage renal disease and were to undergo cadaveric renal transplantation; and nine patients (ASA physical status I and II) without known hepatic or renal disease served as controls. No patient in the liver transplantation group had overt preoperative renal failure, although the glomerular filtration rate was not assessed; the highest serum creatinine level was 1.5 mg/dL in one patient. All patients with renal failure underwent dialysis within 48 h of transplantation. No patient was known to be taking drugs or to have any disease known to affect neuromuscular transmission. Mean age, weight, and selected laboratory data for the three groups are summarized in Table 1.

Anesthesia was induced with thiopental (3–12 mg/kg) and with fentanyl (1–4 μg/kg). Endotracheal intubation was facilitated by the administration of 1–2 mg/kg succinylcholine. Anesthesia was maintained with isoflurane (0.5%–0.8% end-tidal concentration) in N_2O/O_2 or N_2/O_2; incremental doses of fentanyl (1–20 μg/kg) were given if needed. Ventilation was controlled to maintain end-tidal CO_2 between 35 and 40 mm Hg. Blood pressure was monitored directly with the use of an indwelling radial arterial catheter. Body temperature was maintained between 35° and 37.5°C.

After induction of anesthesia, neuromuscular function was monitored by supramaximal stimulation of the ulnar nerve at the wrist with repetitive train-of-four stimuli (2 Hz for 2 s at 10-s intervals) using surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using a Puritan/Bennett Datex (Helsinki, Finland) monitor. After full recovery of neuromuscular transmission from succinylcholine and reestablishment of a baseline evoked response, a single bolus injection of doxacurium (15 μg/kg) was administered through a peripheral intravenous catheter over a 5-s period. The degree of neuromuscular blockade after the administration of doxacurium was described as the percent of control; the height of the first train-of-four response (T_1) was compared with the height of T_1 just before the doxacurium dose. The time from injection of doxacurium to maximum neuromuscular blockade and to 5% (T_5), 25% (T_{25}, also defined as the clinically effective duration of action), 75% (T_{75}), and 95% (T_{95}) recovery of neuromuscular transmission was noted from the tracings.

Blood pressure and heart rate were recorded at 1, 3, and 5 min after administration of the drug. Arterial blood samples (7 mL) were drawn at 0, 2, 4, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, and 360 min after injection of the doxacurium. The transplanted kidney was reperfused in 122 min (±36 min) and the transplanted liver was reperfused in 185 min (±54 min). The blood samples were mixed with ethylenediaminetetraacetic acid and phenylmethylsulfonyl fluoride (a pseudocholinesterase inhibitor) and centrifuged, and the plasma was decanted and frozen to −60°C. Urine was collected from an indwelling urinary catheter for 6–12 h to estimate renal excretion and clearance of doxacurium in those patients undergoing hepatic transplantation and in those patients acting as controls.

Doxacurium concentrations in plasma and in aliquots of urine were later quantified by high-pressure liquid chromatography with appropriate internal

Table 2. Onset, Maximum Blockade, and Clinical Duration of Action for Doxacurium in Patients With or Without Organ Failure

	Patients		
	Control	With hepatic failure	With renal failure
Onset time for maximum blockade (min)	7.8 ± 3.6 ($n = 9$) (2.5–12.7)	10.6 ± 2.2 ($n = 6$) (8.2–13.2)	10.8 ± 5.6 ($n = 7$) (6.3–21.7)
Maximum blockade (%)	86.1 ± 16.8 ($n = 9$) (59–100)	70.4 ± 37.0 ($n = 7$) (0–100)	98.3 ± 2.1 ($n = 7$) (95–100)
T_{25} (min)	36.1 ± 20.6 ($n = 7$) (19.0–79.7)	51.6 ± 29.4 ($n = 4$) (19.5–90.7)	79.6 ± 42.6 ($n = 4$) (28.8–132.7)

Values are mean ± SD (range).

standards (3). The plasma concentrations of doxacurium were used to construct plasma concentration-time profiles for the drug. Plasma doxacurium concentration versus time data were initially analyzed by nonlinear least-squares regression, and pharmacokinetic models of two and three compartments were derived using appropriate best-fit criteria (i.e., least residuals). Model-independent pharmacokinetic variables of mean residence time (MRT), clearance, and volume of distribution at steady state (Vd_{ss}) were also determined from these data using standard formulas based on statistical moment theory (4). The statistical moment variable analogous to half-life ($t_{1/2}$), MRT, represents the time for 63.2% of an administered dose to be eliminated. It was assumed that elimination takes place from the central compartment. The area under the curve (AUC) from time zero to time infinity was estimated by conventional linear trapezoidal summation and from the slope of the terminal exponential phase. The AUC to the last data point averaged 85% of the total area at infinity; it was near 100% for the control group and for the group with hepatic failure. Clearance was calculated by dividing the dose by AUC. The pharmacokinetic and pharmacodynamic data for two patients were eliminated from the hepatic failure group because of inadvertent errors in dosage, and one patient was eliminated from the renal failure group because of preoperative administration of phenytoin.

A one-way analysis of variance with an appropriate multiple-range test was performed to evaluate differences in the calculated variables between the three groups. Statistical significance was assumed at $P < 0.05$.

Results

The mean maximum neuromuscular blockade produced by 15 μg/kg doxacurium was 70.4% for the patients with hepatic failure, 86.1% for the control patients, and 98.3% for the patients with renal failure (Table 2). The range of blockade was largest in those with hepatic failure and narrowest in those with renal failure. There was no significant difference in onset times between the three groups. The mean clinical effective duration (T_{25}) tended to be longer and more variable in the patients with renal failure.

There were no significant differences between systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and heart rate before the administration of doxacurium and the maximum change in these values over a 5-min period between groups (Table 3).

Plots of mean plasma doxacurium concentration versus time data for the three patient groups are presented in Figure 1. At 360 min after its injection, doxacurium could no longer be detected in the plasma from any patient in the control or in the hepatic failure group, and the mean plasma doxacurium concentrations in patients with renal failure had declined to about 90% of the maximum concentration. The mean percentage of the doxacurium dose recovered unchanged from the urine was 30% in patients with hepatic failure and 25% in the control patients. Renal clearance was 0.6 (±0.6) $mL \cdot kg^{-1} \cdot min^{-1}$ in control patients and 0.8 (±0.7) $mL \cdot kg^{-1} \cdot min^{-1}$ in those with hepatic failure. Renal clearance could not be calculated for the anephric patients.

Preliminary compartmental modeling of plasma doxacurium concentrations in individual patients over time showed a triphasic pattern in 18 patients, a biphasic pattern in four patients, and a poorly defined pattern in two patients. Noncompartmental methods were, therefore, used for the final analysis of pharmacokinetic data from the individual patients and of summary data from the patient groups. The pharmacokinetic variables derived from these data

Table 3. Changes in Cardiovascular Variables After Administration of Doxacurium in Patients With or Without Organ Failure

	Control patients ($n = 7$)		Patients with hepatic failure ($n = 8$)		Patients with renal failure ($n = 8$)	
	Preinjection value	Value at time of maximum change within 5 min postinjection	Preinjection value	Value at time of maximum change within 5 min postinjection	Preinjection value	Value at time of maximum change within 5 min postinjection
Arterial blood pressure (mm Hg)						
Systolic	115 ± 29	111 ± 32	109 ± 26	110 ± 22	117 ± 35	116 ± 32
Diastolic	68 ± 17	66 ± 20	59 ± 13	61 ± 14	60 ± 17	58 ± 18
Mean	84 ± 21	82 ± 25	75 ± 17	77 ± 16	79 ± 22	77 ± 22
Heart rate (beats/min)	73 ± 11	72 ± 11	78 ± 8	77 ± 7	79 ± 13	80 ± 12

Values are mean ± SD.

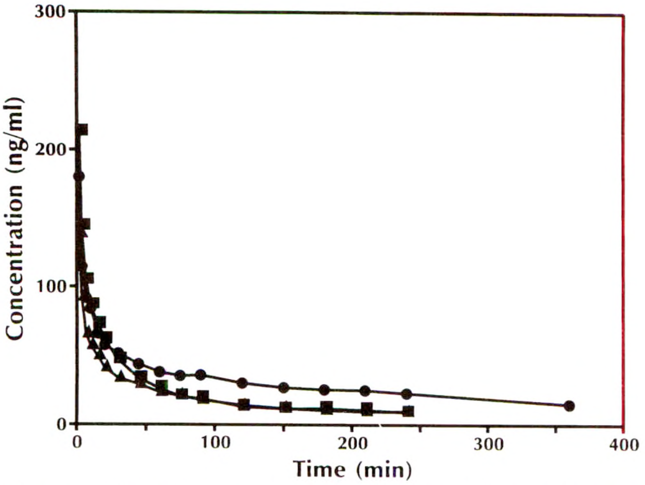


Figure 1. Mean plasma concentrations of doxacurium (▲, patients with liver transplantation, $n = 7$; ●, with renal transplantation, $n = 8$; ■, elective surgery, $n = 9$).

are shown in Table 4. Patients without renal function demonstrated a significantly greater AUC, significantly longer MRT, and significantly lower clearance rate than patients with normal renal function. These patients also had a significantly greater AUC and MRT than those with hepatic failure. Vd_{ss} did not differ significantly between the three groups. There was no correlation between pharmacokinetic variables and serum albumin, γ-glutamyl transpeptidase, and creatinine levels.

Discussion

This study was designed to evaluate the influence of hepatic failure and renal failure on the pharmacodynamics and pharmacokinetics of a given dose of doxacurium. The dose of doxacurium used (15 μg/kg) was estimated to be the ED_{95} for neuromuscular blockade during nitrous oxide-isoflurane anesthesia. This dose of doxacurium produced a wide range of neuromuscular blockade in the patients with hepatic failure (mean, 70%) and in control patients (mean, 86.1%), but a more narrow range of blockade in the patients with renal failure (mean, 98%). Thus, we underestimated the ED_{95} in normal patients and in those with hepatic disease. A supplemental dose of doxacurium in patients with less than 95% blockade would have resulted in more intense and more uniform neuromuscular blockade and would have allowed us to estimate more closely the recovery times after doxacurium in the three groups. However, supplemental dosing would have complicated the pharmacokinetic curve-fitting procedure. In addition, although a higher bolus dose of doxacurium would have resulted in complete neuromuscular blockade in a larger number of patients in all groups, recovery endpoints would have been difficult to compare, because equal doses of relaxant were not administered. Onset times were similar for the three groups of patients. The times between onset of action and maximum blockade at a low dose that we found are in agreement with those reported in other studies and confirm the relatively slow onset of this drug (1,5). There were minimal cardiovascular effects associated with the administration of doxacurium.

The clinically useful duration of action (T_{25}) of doxacurium was markedly but not statistically longer in the group with renal failure than in the control group. The duration of action of doxacurium was more variable in the group with renal failure. Similar findings have been noted by others in patients with renal failure (5).

The ED_{95} of a relaxant could be defined as the product of Vd_{ss} and the sensitivity of the neuromus-

Table 4. Pharmacokinetic Variables for Doxacurium in Patients With or Without Organ Failure

	Patients		
	Control (n = 9)	With hepatic failure (n = 7)	With renal failure (n = 8)
AUC ($\text{ng}\cdot\text{min}\cdot\text{mL}^{-1}$)	6,837 ± 2,523	6,647 ± 930	15,534 ± 7,930^{a,b}
Cl ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	2.7 ± 1.6	2.3 ± 0.4	1.2 ± 0.7^{a}
Vd_{ss} (mL/kg)	220 ± 110	290 ± 60	270 ± 130
$t_{1/2}$ (min)	99 ± 54	115 ± 31	221 ± 156
MRT (min)	95.2 ± 57	129.4 ± 30	270 ± 210^{a,b}

AUC, area under the curve; Cl, clearance; MRT, mean residence time; Vd_{ss}, volume of distribution at steady state.
All values are mean ± SD.
[a] Different from control values (analysis of variance).
[b] Different from hepatic failure group (analysis of variance).

cular receptor to the drug (CP_{ss95}). Pathophysiologic changes associated with liver or renal disease frequently alter the protein binding and volumes in which drugs distribute. Renal dialysis can also influence drug distribution. Vd_{ss} did not differ significantly in the three patient groups. The volume of distribution of doxacurium was in excess of the extracellular fluid volumes and tended to be higher in patients with organ failure. There was no correlation between serum albumin levels and Vd_{ss}.

We found that doxacurium disappears more slowly from the plasma of patients with renal failure. This results in plasma doxacurium concentrations that from 30 to 360 min are higher in patients with renal failure than in the other groups of patients. The transplanted kidney was reperfused and was producing urine during this time period. We could not identify any specific change in the plasma decay curve of doxacurium associated with revascularization of the transplanted kidney. Mean plasma concentrations of doxacurium were at the lower level of sensitivity for detection in normal patients and in those with hepatic failure by 240 min. Patients with renal failure had significantly larger AUC, longer MRT, and smaller plasma clearance than did control patients and had greater AUC and MRT than did patients with liver failure. Our data show that about 30% of doxacurium is excreted unchanged in the urine within 12 h; similar findings have been reported by others (1). Thus, it is not surprising that renal failure adversely influences the kinetics of doxacurium. Disposition studies in cats have shown that doxacurium is eliminated largely unchanged in the urine and bile (Welch RM, Loebf P, Maehr R, DeAngelis R; unpublished data). Alternative pathways through the liver for clearance of doxacurium may exist in the cat, but such pathways are undocumented in humans.

There are many examples of delayed elimination of long-acting neuromuscular blocking agents owing to renal impairment. A study of pancuronium in patients with chronic renal failure demonstrated a significantly longer elimination half-life (>300% increase) and an increased volume of distribution when compared with healthy patients (6). A study of metocurine in patients during kidney transplant operation showed a significantly decreased plasma metocurine clearance and a significantly longer elimination half-life (~90% increase) compared with values in healthy patients (7). Vecuronium or pipecuronium has a significantly lower clearance and a longer elimination half-life in patients with renal failure than in patients with normal renal function (8–10).

Significant differences were not detected between the pharmacokinetic values in patients with liver transplants and in control patients. The mean plasma doxacurium concentrations are identical (Figure 1) from about 45 to 240 min in these two groups. Most of the plasma samples were collected before the anhepatic period and before significant blood volume replacement (i.e., <10% blood volume replacement). Hence, liver disease appears to have no significant impact on the pharmacokinetics of doxacurium. Liver disease reduces the clearance of both pancuronium and vecuronium, which are eliminated through metabolism in addition to renal and biliary excretion of unchanged drug. Somogyi et al. (11) noted that pancuronium plasma clearance was reduced by more than 50% in patients with biliary obstruction. Patients with hepatic cirrhosis demonstrated an approximate doubling of both the volume of distribution and the elimination half-life of pancuronium (12). Vecuronium plasma clearance was reduced significantly and the elimination half-life was prolonged in patients with cirrhosis (13).

In conclusion, doxacurium has a longer duration of action in patients with liver or kidney failure than in normal patients. Renal excretion of unchanged drug is an important elimination route for doxacurium. Patients with renal dysfunction tend to clear doxacurium at a slower rate than normal patients do; therefore, the duration of action in patients with renal dysfunction can be expected to be prolonged and be more variable.

References

1. Basta SJ, Savarese JJ, Ali HH, et al. Clinical pharmacology of doxacurium chloride. A new long-acting nondepolarizing muscle relaxant. Anesthesiology 1988;69:478–86.
2. Lennon RL, Hosking MP, Houck PC, et al. Doxacurium chloride for neuromuscular blockade before tracheal intubation and surgery during nitrous oxide-oxygen-narcotic-enflurane anesthesia. Anesth Analg 1989;68:255–60.
3. DeAngelis R, Loebs P, Maehr R, Saverese J, Welch R. High performance liquid chromatography analysis of doxacurium—a new long-acting neuromuscular blocker. J Chromatogr 1990;525:389–400.
4. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Dekker, 1982:409–17.
5. Cashman JN, Luke JJ, Jones RM. Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function. Br J Anaesth 1990;64:186–92.
6. McLeod K, Watson MJ, Rowlins MD. Pharmacokinetics of pancuronium in patients with normal and impaired renal function. Br J Anaesth 1976;48:341–5.
7. Brotherton WP, Matteo RS. Pharmacokinetics and pharmacodynamics of metocurine in humans with or without renal failure. Anesthesiology 1981;55:273–6.
8. Lynam DP, Cronnelly R, Castagnoli KP, et al. The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. Anesthesiology 1988;69:227–31.
9. Caldwell JE, Canfell PC, Castagnoli KP, et al. The influence of renal failure on the pharmacokinetics and duration of action of pipecuronium bromide in patients anesthetized with halothane and nitrous oxide. Anesthesiology 1989;70:7–12.
10. Meistelman C, Leinhart A, Leveque C, Bitker MO, Pigot B. Pharmacology of vecuronium in patients with end-stage renal failure. Anesthesiology 1983;59:A293.
11. Somogyi AA, Shanks CA, Triggs EJ. Disposition kinetics of pancuronium bromide in patients with total biliary obstruction. Br J Anaesth 1977;49:1103–8.
12. Duvaldestin P, Agonston S, Henzel D, Kersten UW, Desmonts JM. Pancuronium pharmacokinetics in patients with liver cirrhosis. Br J Anaesth 1978;50:1131–6.
13. Lebrault C, Berger JL, D'Hollander AA, Gomeni R, Henzel D, Duvaldestin P. Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. Anesthesiology 1985;62:601–5.

ANESTH ANALG 1991;72:151–60

Masseter Muscle Spasm in Children: Implications of Continuing the Triggering Anesthetic

Judith A. Littleford, BSc, MD, Leena R. Patel, MD, FRCPC, Deepak Bose, MD, PhD, Cal B. Cameron, MD, FRCPC, and Cheryl McKillop, RRT

LITTLEFORD JA, PATEL LR, BOSE D, CAMERON CB, McKILLOP C. Masseter muscle spasm in children: implications of continuing the triggering anesthetic. Anesth Analg 1991;72:151–60.

This retrospective study was undertaken to examine the management and outcome of children who developed isolated masseter muscle spasm (MMS) after the administration of intravenous succinylcholine during anesthetic induction. The inhalation anesthetics used for induction were continued in all of these cases. The medical records of 68 patients (male/female ratio, 1.7:1), identified from approximately 42,000 anesthetics given during the period 1980–1989, were reviewed. Fifty-seven children (2.3–12 yr old) were diagnosed as having isolated MMS, i.e., MMS without spasm of other muscles; 11 experienced generalized rigidity in combination with MMS. Anesthetic and postoperative management of these two groups differed. The overall incidence of MMS was 0.3% of inhalation anesthetics during which succinylcholine was given.

Intraoperative arrhythmias occurred in 33% of the patients who developed isolated MMS and more frequently in older children. Most children experienced some degree of hypercarbia and/or metabolic acidosis, but the significance of these abnormalities in the spontaneously ventilating, fasting child is unknown. Serum creatine kinase levels when measured 18–24 h postoperatively were elevated in all but one child (n = 45). There was no long-term morbidity and no mortality. We conclude that failure of the masseter muscles to relax after succinylcholine is not uncommon in children. Based on our experience, and accepting that MMS may be part of the clinical spectrum of malignant hyperthermia, we believe that anesthesia can be continued safely in cases of isolated MMS when careful monitoring accompanies diagnostic evaluation. This differs from the current practice of discontinuing the anesthetic or switching to a nontriggering anesthetic technique.

Key Words: ANESTHESIA, PEDIATRIC. MUSCLE, SKELETAL—masseter. ANESTHETICS, VOLATILE—halothane. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE. HYPERTHERMIA, MALIGNANT—diagnostic signs.

The significance of masseter muscle spasm (MMS) occurring in children who have received intravenous succinylcholine during anesthetic induction is undergoing reevaluation (1). Based on previously documented associations between MMS and malignant hyperthermia (MH) (2–4), the dominant approach has been to proceed as if the patient was at imminent risk for developing MH and either to modify the anesthetic technique to exclude known triggering agents (5) or to discontinue anesthesia, with or without dantrolene administration (6).

Masseter spasm can occur in isolation, however, without progression to the hypermetabolic state characterized by MH (7). Recent investigations have revealed a differential effect of succinylcholine on human masticatory and limb muscles (8). In addition, preexposure of normal skeletal muscle to halothane in vitro has been shown to increase the magnitude of a succinylcholine-induced contracture response (9).

Masseter muscle spasm has been reported in retrospective reviews to occur in approximately 1% of pediatric anesthetics involving halothane and succinylcholine (10,11). In the first of these reviews, the anesthetic was either abandoned or switched to a nontriggering technique, whereas in the second report anesthesia was continued uneventfully in 75% of the cases, and abandoned or switched in the remaining 25%. However, each series contained a limited number of patients.

This report analyzes our experience in all cases of

Received from the Department of Anesthesia, University of Manitoba, Winnipeg, Canada. Accepted for publication September 7, 1990.

Address correspondence to Dr. Patel, Section of Pediatric Anaesthesia, Department of Anaesthesia, Children's Hospital, 840 Sherbrook Street, Winnipeg, Canada R3A 1S1.

©1991 by the International Anesthesia Research Society

masseter spasm identified during a 10-yr period, concentrating on the outcome of children who developed isolated MMS and in whom the same anesthetic was continued.

The objectives of this study were (a) to document the incidence of MMS at the Winnipeg Children's Hospital for the period of 1980 through 1989; (b) to examine the management and outcome of children who developed isolated MMS or generalized rigidity in combination with MMS; (c) to evaluate our present anesthetic practice in these cases; and (d) to describe conditions under which it might be considered safe to continue the same anesthetic.

Methods

The medical records of children who experienced MMS on induction of anesthesia between 1980 and 1989 inclusive were reviewed retrospectively. Cases were identified from an in-hospital registry previously compiled by all of the anesthesiologists ($n = 8$) who practiced at the Winnipeg Children's Hospital during the years encompassed by this study. This registry was formalized in 1982 under the auspices of the Pediatric Anesthesia Follow-up Program (12), thus providing reasonable assurance that all cases of masseter spasm would be identified over the 10-yr period of interest.

The Follow-up Program is a formalized method of collecting and processing information pertaining to each child anesthetized at this institution. Details of the anesthetic and coexisting medical conditions, as well as the occurrence of anesthetic-related events, are recorded on a standardized form by the attending anesthesiologist. Postoperative follow-up information is added to the form by designated anesthesia personnel. These same personnel also review the patients' charts and conduct a patient/parent interview to ensure the accuracy and completeness of the recorded information. The form is returned to the anesthesiologist for final review before data processing. Because the anesthesiologists' billing card is incorporated into the anesthesia record and follow-up form requiring that both be filled out simultaneously, there is 100% compliance with the program.

Demographic, anesthetic, and morbidity data for the entire pediatric surgical population were supplied by the Follow-up Program for the years 1982 through 1989. Information provided by the program was extrapolated to obtain an estimate of the total number of anesthetics and those involving a volatile agent plus succinylcholine given during 1980 and 1981. The calculated 10-yr incidence was verified using only the data from 1982 through 1989, and was found to be the same.

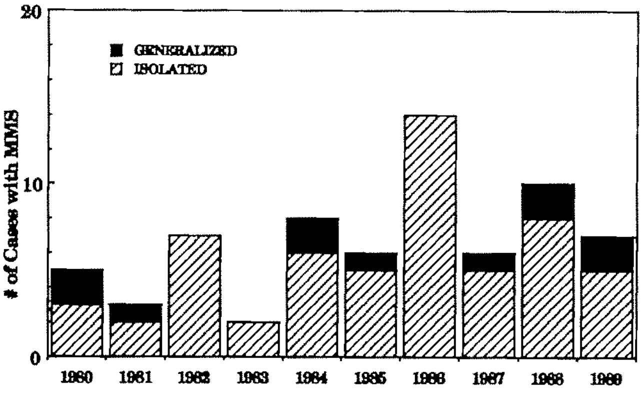


Figure 1. Number of cases of masseter muscle spasm by year.

All members of the anesthesia practice group agreed to establish a clinical diagnosis of "masseter spasm," if an obvious increase in resistance to mouth-opening occurred, creating a transient impediment to tracheal intubation, despite the administration of what was considered to be an adequate relaxant dose of intravenous succinylcholine. The term "isolated masseter spasm" was reserved for tightness confined to the muscles of mastication; MMS that occurred in combination with limb or chest rigidity was denoted as generalized rigidity.

χ^2-Analysis was used to compare proportions between groups. A two-sample t-test was used when the variations were homogenous. Nonparametric tests, such as the Wilcoxon rank sum test, were used with highly skewed distributions. For very rare events, the comparisons were done using the Poisson goodness-of-fit test. The Pearson correlation coefficient was applied to assess the association between duration of surgery and creatine kinase (CK) values. The exploratory nature of this study necessitated multiple comparisons; therefore, the significance level was set at $\alpha = 0.01$ to avoid spuriously significant results.

Results

Sixty-eight cases of MMS were identified during the years 1980–1989 (Figure 1). Approximately 42,000 anesthetics were administered in that same period; 54% involved an inhalation induction followed by succinylcholine administration. This represents an incidence of MMS of 0.16% of all anesthetics administered and 0.3% of the anesthetics in which a volatile

Table 1. Demographic Data

	Younger children ($n = 29$)			Older children ($n = 28$)		
	Mean	Range	Median	Mean	Range	Median
Age (yr)	3.7	2.3–5.0	3.3	7.9	5.3–12.0	7.5
Weight (kg)	16.3	10.5–26.1	15.5	26.3	14.0–44.0	23.9
Height (cm)	100	85–118	97	123	104–154	120
Sex						
Male		17			19	
Female		12			9	

agent was used in combination with intravenous succinylcholine during induction.

Eleven children were diagnosed with generalized rigidity in addition to MMS. Data pertaining to these cases are summarized separately, as the perioperative management differed considerably from that of the 57 isolated MMS cases.

Isolated Masseter Spasm Cases

The children were divided into two groups based on age (≤5 yr, >5 yr). This separation reflects the fact that anesthetic morbidity and mortality differs in younger from that in older children at this institution (12).

The characteristics of the children in the study are seen in Tables 1 and 2. The male-to-female ratio was 1.7 to 1. No child was less than 2 yr or more than 12 yr old. The vast majority were judged to be healthy both in terms of physical status (98% being ASA I or II) and coexisting medical conditions (81% having none). None was suspected of being MH-susceptible on the basis of preoperative evaluation. Dental operations were the most commonly performed procedures in the younger children, whereas ear-nose-throat procedures dominated in the older age group (χ^2-test, $P < 0.01$). Younger children were more likely to be treated as outpatients. The duration of surgery was longer in the younger children (Student's t-test, $P < 0.01$). This was related to the surgical procedure. Twenty-three percent ($n = 13$) of the patients had at least one uneventful prior surgery involving a volatile anesthetic, succinylcholine, or a combination of the two.

All patients were monitored with electrocardiogram, precordial stethoscope, and a noninvasive method of measuring blood pressure. Temperature and oxyhemoglobin saturation (Sa_{O_2}) were measured in 91% and 28% of cases, respectively. Routine Sa_{O_2} monitoring was instituted in 1987. End-tidal CO_2 (ET_{CO_2}) monitoring was not routinely available at this institution during the study period.

Table 2. Surgical Data

	Younger children ($n = 29$)	Older children ($n = 28$)
Duration of surgery (h)		
Mean	1.0	0.6
Range	0.2–3.1	0.2–1.6
Median	0.8	0.6
ASA physical status		
I	26	23
II	2	5
III	1	0
Emergency	3	1
Procedure		
Dental	17[a]	5
ENT	6	13
Orthopedic	3	4
Urologic	1	3
Eye	1	1
Plastic	0	2
Other	1	0
Status[b]		
Outpatient	18	7
Inpatient	7	15
Same-day admit	4	6
Previous surgery	4	9
Pertinent history[c]	4	7

ENT, ear, nose, throat.

[a] χ^2 Test, $P < 0.01$, comparing frequency of dental procedures in younger children to similarly aged patients in entire pediatric surgical population.

[b] χ^2 Test, $P < 0.01$, comparing frequency of outpatient, inpatient, and same-day admit for younger versus older children.

[c] Including one or more of coexisting infection, neuromuscular/skeletal disorder, follow-up family history of sudden infant death syndrome/malignant hyperthermia.

Atropine was administered preoperatively (intramuscularly) or with induction (intravenously) to 90% of the younger children (Table 3), and to a majority (68%) of older children. As a result of the pharmacologic effect of atropine on heart rate, the heart rate increase reported is that which occurred subsequent to any change in the rate induced by this drug. Two children received a narcotic preoperatively.

Almost all of the younger children (97%) underwent mask induction with halothane. Intravenous induction with thiopental was reserved for cases

Table 3. Anesthesia/Perioperative Period

	Younger children (n = 29)	Older children (n = 28)
Atropine	26	19
Induction		
Mask	28	24
Intravenous	1	4
Halothane	29	27
Switch from halothane to another volatile agent	4	8
Spontaneous ventilation	29	28
Succinylcholine (mg/kg)		
Mean	1.2	1.2
Range	0.9–2.4	1.0–2.0
Median	1.0	1.2
Increase in heart rate (beats/min)[a]	21	20
Increase in systolic BP (mm Hg)[a]	14	15
Increase in temperature (°C)[a,b]	0.4	0.3
Signs and symptoms		
Arrhythmia[c]	5	14
Diaphoresis	1	0
Tachypnea	0	1
PO myalgia	1	4[d]
PO temperature[e,f]	7	9
PO vomiting	4	8

BP, blood pressure; PO, postoperative.

[a] Mean increase in heart rate, systolic BP, and temperature measured from induction of anesthesia to termination of the surgical procedure.

[b] Increase in temperature, all routes (oral, axilla, rectal).

[c] χ^2 Test, $P < 0.01$, comparing frequency of arrhythmia for younger versus older children.

[d] Poisson test, $P < 0.01$, comparing frequency of PO myalgia in older children with isolated masseter muscle spasm to similarly aged children in entire pediatric surgical population.

[e] PO temperature defined as >37°C axilla, >37.5°C oral, >38°C rectal.

[f] χ^2 Test, $P < 0.01$, comparing frequency of PO temperature in all children with isolated masseter muscle spasm to similarly aged children in entire pediatric surgical population.

requiring a rapid-sequence technique. A defasciculating dose of *d*-tubocurarine was administered to four patients. The difficulties experienced in overcoming resistance to mouth-opening varied in degree and duration, but eventually intubation was achieved in all cases. The dose of intravenous succinylcholine used to facilitate intubation was similar in both age groups (Table 3). The interval between succinylcholine administration and onset of MMS was occasionally recorded as either immediate or within 1–2 min but this information was missing in the majority of patients, as was duration of the spasm.

All children breathed spontaneously during maintenance anesthesia with nitrous oxide in oxygen and a volatile agent. Intraoperative narcotics were used sparingly (four cases); one child received droperidol before emergence. No other anesthetic agents, except for those already mentioned, were administered.

Intraoperative arrhythmias (including premature ventricular contractions, multifocal premature ventricular contractions, bigeminy, or premature atrial contractions) occurred in 33% of the cases and more frequently in older children (Table 3). In the anesthesiologists' notes, all arrhythmias were said to have responded to manual hyperventilation with 100% oxygen and/or a change in volatile agent. Early increases in heart rate and blood pressure were attributed to surgical stimulation during a light plane of anesthesia.

Within the first 24 h postoperatively, 28% of the children had an increase in temperature above the generally accepted normal values of 36.5°C axilla, 37°C oral, or 37.5°C rectal: 63% of these were considered to represent low-grade temperatures (within 1°C of normal) and no drug treatment was given. Postoperative increases in temperature were more prevalent in our patients than in patients of similar ages in the entire pediatric surgical population (Table 3). Nine of the 19 children who underwent ear-nose-throat surgery had postoperative fevers. The remainder of fevers were distributed randomly among the procedures and age groups.

In general, evaluation of individual patients using biochemical parameters became more complete over the years of the study. Currently we monitor vital signs, muscle tone, and continuous electrocardiogram intraoperatively, and draw blood samples for immediate measurement of blood gas tensions and levels of electrolytes and CK. Postoperative urine myoglobin (first voided specimen) and repeat CK measurements (18–24 h) are obtained. Table 4 lists selected perioperative laboratory results, chosen for their relevance to the topic under study. Values for Po_2 or Sao_2 are not included in the table; however, all children remained well oxygenated by these two criteria, and no episodes of cyanosis or mottling were reported with inspired oxygen concentrations ranging from 33% to 100%.

The blood gas tensions were similar in our two age groups with isolated MMS. Younger children tended to have higher intraoperative CK levels than older children, whereas older children tended to have higher postoperative CK levels (obtained 18–24 h postoperatively) than younger children. These differences between the two age groups did not reach statistical significance. The duration of surgery did not influence the peak CK values. Serum and/or urine myoglobin were measured using a variety of techniques throughout the decade, which renders an overall comment on quantitative analysis difficult; a positive result indicates that myoglobin was detected. The results were positive in 14 younger children (n = 29, not measured in 10 cases) and six older children (n = 28, not measured in 18 cases) (Table 4). Serum

Table 4. Intraoperative and Postoperative Laboratory Results

	Younger children (n = 29)				Older children (n = 28)			
	Mean	Range	Median	n	Mean	Range	Median	n
Blood sample								
Arterial				14				11
Venous				2				3
Capillary				10				8
Blood								
Pco_2 (mm Hg)	50	33–64	49	27	52	26–88	49	24
pH	7.24	7.12–7.51	7.23	27	7.25	7.12–7.40	7.24	24
Base deficit (mEq/L)	6.7	2.8–10.9	6.7	22	5.81	3.0–9.0	5.8	20
CK (U/L)[a]								
Intraoperative	845	158–6,100	356	22	546	68–3,130	272	18
18–24 h	10,678	279–66,880	4,752	20	19,080	1,425–138,240	7,640	16
K^+ (mmol/L)[b]	4.1	3.5–5.0	4.1	14	4.2	3.6–4.5	4.2	10
Myoglobin: urine/serum								
Positive				14				6
Negative				5				4
Not done				10				18

CK, creatine kinase.

[a] CK normal, 36–188 U/L before 1988, 0–165 U/L from 1988 on.

[b] K^+ normal, 3.5–5.3 mmol/L.

Table 5. Observation Times

	Younger children (n = 29)				Older children (n =28)			
	Mean	Range	Median	n	Mean	Range	Median	n
Anesthesia (h)	1.5	0.6–3.3	1.4		1.2	0.7–2.3	1.1	
PARR (h)	1.0	0.4–4.4	0.8[a]		1.3	0.6–4.3	1.1	
Outpatient unit (h)	2.9	1.7–5.2	2.5	18	3.7	2.1–6.3	2.9	7
Inpatient unit (h)	52.0	19.0–216	43	11	53.0	6.0–240	24.0	21
Total observation time for outpatients (h)[b]	5.2				6.1			
Total observation time for inpatients (h)[b]	55.2				56.1			

PARR, postanesthesia recovery room.

[a] Wilcoxon test, $P < 0.01$, comparing time in PARR for younger versus older children.

[b] Total observation time represents time from induction of anesthesia to discharge from hospital.

potassium values were normal in all children in whom K^+ data were recorded (n = 24).

The postoperative time period during which a child who developed isolated MMS was under direct observation by hospital personnel varied considerably, in terms of the length of stay in both the postanesthesia recovery room and the outpatient surgery unit (Table 5). Suffice it to say that certain criteria must be fulfilled before discharge from the latter (i.e., tolerating fluids, pain under control, voided, vital signs stable, parent or guardian in accompaniment, alert). Three of the children originally scheduled as outpatients were admitted for overnight observation (included with same-day admit, Table 2) at the anesthesiologist's discretion. The average hospital stay for inpatients was 2.5 days (Table 5).

When MMS developed it was discussed with all parents. Instructions were given to the parents of outpatients to return with their child for additional evaluation in the event of postoperative fever, discolored urine, stiffness, or muscle pain. Appointments for 24-h CK determinations were arranged. A follow-up telephone interview (within 24 h) conducted by outpatient day surgery nurses or an in-hospital visit (within 72 h) by a designated anesthesia follow-up nurse is common practice at our institution to learn of any postoperative events and to assess the level of satisfaction with the anesthesia.

Five of the 57 children who developed isolated MMS each had one subsequent uneventful anesthetic during the study period, involving a halothane mask induction followed by spontaneous ventilation during maintenance anesthesia with nitrous oxide in oxygen and halothane.

Table 6. Profiles of Patients Developing Generalized Rigidity

Procedure	Age (yr)[a]	Sex	Outcome	P_{CO_2} (mm Hg)	pH	Base deficit (mEq/L)	K^+ (mmol/L)[b]	Urine myoglobin	IO CK (U/L)	18–24-h CK (U/L)[c]
Dental	3.5	F	Continued	57	7.16	9.5	5.2	+	412	96,400
ENT	2.7	M	Continued	46	7.16	11.0	5.0	+	1,340	79,400
Dental[d]	2.8	F	Aborted	36	7.25	10.2	3.7	+	579	74,800
Dental	1.3	M	Continued	64	7.11	11.1	5.6	+	597	79,000
ENT	5.9	M	Continued	65	7.12	10.1	4.3	+	828	109,368
ENT	7.5	M	Aborted	59	7.27	1.2	4.4	–	8,520	
Eye[d]	2.4	F	Aborted	41	7.31	5.0	4.4	+	584	28,120
ENT	2.1	M	Aborted	27	7.32		5.1	+	390	46,650
Orthopedic	2.2	M	Switched							184,200
Orthopedic[d]	12.3	M	Switched	31	7.23	13.0		+		
Orthopedic[d]	0.2	F	Switched	28	7.49	+0.5	5.8	+	208	134
Mean	3.9			45	7.24	7.8	4.7		1,495	77,564
Median	2.6			41	7.23	9.8	4.7		582	76,900

P_{CO_2}, carbon dioxide pressure; IO, intraoperative; CK, creatine kinase; ENT, ear, nose, throat.

The following tests refer to comparisons of these data in patients with generalized rigidity versus data from patients with isolated masseter muscle spasm.

[a] Wilcoxon test, $P < 0.01$.

[b] Wilcoxon test, $P < 0.01$.

[c] Wilcoxon test, $P < 0.01$.

[d] Received dantrolene.

Generalized Rigidity Cases

Eleven patients exhibited generalized rigidity in response to intravenous succinylcholine (mean dose, 1.4 mg/kg). All had undergone mask induction with halothane. The youngest and the oldest of all MMS patients were found in this group (Table 6). The children were ASA I or II, predominantly young (≤5 yr) and more frequently male. Five of the 11 patients had a history of neuromuscular or skeletal abnormalities, including cerebral palsy, scoliosis, clubfeet, strabismus, and possible congenital myopathy. Extensive questioning of families postoperatively revealed an additional three with distant relatives who had histories suggestive of MH. The presence of a previous history, including a neuromuscular/skeletal disorder or a follow-up family history of MH, was statistically significantly when compared with the isolated MMS group of patients (χ^2-test, $P < 0.01$).

One child had a prior uneventful general anesthetic with halothane alone. In follow-up correspondence, it was learned that a second child had developed masseter spasm (general muscle tone was not assessed) at a different institution during a previous inhalation anesthetic where succinylcholine was given.

Three children received atropine preoperatively, and an additional six received the drug with induction. No other premedicants were given.

The frequency of intraoperative arrhythmias was similar to that in the isolated MMS group. The skin coloring of one child was described as mottled. Tachypnea developed in two others. Five of the 11 children were admitted directly to the intensive care unit. Six of the 11 children received follow-up care in an inpatient unit. Four patients were given dantrolene. The highest recorded postoperative temperature in these 11 patients was 38.5°C (rectal).

Mean pH was similar in the isolated and generalized rigidity groups; P_{CO_2} tended to be lower in the latter, which is most likely a reflection of positive pressure ventilation instituted in the majority of patients who developed generalized rigidity. The postoperative CK levels were higher in the generalized rigidity group than in the isolated MMS group (Table 6). Of the 10 specimens tested, urine myoglobin was positive in nine and negative in one. Potassium levels were higher when compared with the isolated MMS values.

None of the 11 children who developed generalized rigidity had a subsequent anesthetic involving a volatile agent, succinylcholine, or a combination of the two at our institution during the study period.

There were no deaths in the 68 cases of MMS. All children were found to have had an uneventful postoperative course.

Discussion

Masseter spasm during anesthesia, especially during induction, occurs in patients of all ages, but more commonly in children. One investigator speculated that MMS may represent the clinical expression of a benign pharmacologic response to depolarizing relaxants (8). Another commented that "it is very difficult to determine the difference between an exaggerated normal response to succinylcholine and a pathologic response in which the increase in masseter tone may herald MH susceptibility" (13).

The differential diagnosis of masseter spasm includes (a) an insufficient dose of succinylcholine resulting in inadequate relaxation; (b) overzealous interpretation of mild jaw tightness as MMS; (c) normal pharmacodynamic action of succinylcholine on masseter muscle; (d) synergistic clinical interaction between succinylcholine and halothane; (e) underlying myopathy; and (f) MH. The following discussion considers each of these six possibilities as they relate to our clinical observations.

Cook and Fischer suggested that the degree of neuromuscular blockade achieved in children for a given dose of succinylcholine is related to body surface area (14). They attributed this to age-related differences in extracellular fluid volume and used it to explain the apparent resistance of children to succinylcholine: the younger the child, the greater the amount of drug required on a weight basis to produce clinical relaxation comparable to that obtained in adults.

This relationship between age and succinylcholine response has been quantified in pediatric patients undergoing thiopental-fentanyl-nitrous oxide anesthesia (15). Using intravenous succinylcholine to suppress the adductor pollicis twitch response to supramaximal ulnar nerve stimulation, Meakin et al. calculated an ED_{90} and ED_{95} of 0.352 and 0.423 mg/kg, respectively, in children aged 1–5 yr. Because these values are greater than the ED_{90} (0.29 mg/kg) in adults (16), inadequate neuromuscular blockade has been implicated as a factor contributing to the difficulties experienced in intubating children with succinylcholine (17).

The preceding data stand in contrast to the results of two more recent studies in children. In one of these, complete relaxation of the masseter and adductor pollicis muscles was achieved in all children using a 1-mg/kg intravenous dose of succinylcholine (18). In the other, complete inhibition of neuromuscular transmission in the adductor pollicis was associated with intravenous succinylcholine doses of 1.5 mg/kg in children aged 2–13 yr (19). In our series, the doses of succinylcholine ranged from 0.9 to 2.4 mg/kg, with a mean dose of 1.2 mg/kg in children who developed isolated MMS (Table 3). Because our dosage levels are consistent with the commonly accepted dosing recommendations in the literature, it is likely that the amount of succinylcholine administered to the children in our study was sufficient to achieve relaxation, thus satisfying one component of our definition of masseter spasm. It is not possible to determine this with complete certainty, however, because we did not use electromyographic monitors to assess the degree of neuromuscular blockade before intubation.

A more fundamental controversy exists as to the definition of MMS as distinct from incomplete relaxation of the jaw. Rosenberg suggested that verification by a second anesthesiologist, together with confirmation of rhabdomyolysis, would provide more convincing evidence of trismus (20). This may be useful in large centers, but it seems excessive in our situation. Members of our anesthesia practice group did agree to use a common definition of MMS, and, given the small number of anesthesiologists involved, a uniform approach is more easily achieved. At least one appeal has been made to encourage the routine use of objective measures of masseter spasm in an attempt to reduce the interobserver variability inherent in a diagnosis based on subjective criteria (21).

Two retrospective studies in pediatric patients found MMS in about 0.8% and 1% of all anesthetics that involved halothane and succinylcholine, respectively (10,11). Using a different study design, Ording reported an incidence of MMS of 1 in 12,000 anesthetics in Denmark in the period 1978–1984 (22). The study included adults and children who underwent anesthesia induction with a variety of techniques. Our incidence of 0.3% is less than the reported experience with children (10,11). This may be due in part to our having a definition that discounted cases of "mild incomplete jaw relaxation."

The third theory to explain MMS deals with the action of succinylcholine on masseter muscles. In a study conducted by Van Der Spek et al., all children receiving succinylcholine during halothane anesthesia responded with a reduction in mouth-opening and an increase in jaw stiffness at a time when their limb muscles were fully relaxed (8). This finding has been confirmed by Saddler and coworkers (18). The implications of this routine pharmacologic response serve to confuse further the relationship between MMS and MH.

Fletcher and Rosenberg attempted to define the observed clinical interaction between succinylcholine and halothane with in vitro testing using skeletal muscle biopsy specimens taken from people being investigated for MH susceptibility, including those with and those without a history of MMS. They concluded that when halothane was used, succinylcholine could produce contractures in normal skeletal muscle (9). What mediates the synergism observed is unknown, but speculations include succinylcholine-induced stimulation of phospholipase A_2 activity in skeletal muscle (23). Our practice of mask inductions with halothane would tend to set the stage for contractures after succinylcholine is given.

Certain recognized myopathic processes may predispose the patient to develop muscle rigidity during anesthesia (24). In some cases, the rigidity has been confined to the masseter muscles and anesthesia continued uneventfully. Whether or not these patients are at increased risk for developing MH is a matter of controversy (25).

Finally, many would suggest quite simply that MMS equals MH based on a convincing 50%–60% occurrence of positive muscle biopsy tests for MH susceptibility in MMS patients (2,3,26). This correlation should be viewed with the understanding that uniform standards for contracture testing have only recently been published (27,28). Differences exist between the protocols adopted by European and by North American centers. In addition, patients with various muscle disorders (e.g., Duchenne muscular dystrophy, central core disease) and the absence of personal or family history of MH sometimes show a positive contracture response (24,25). It remains to be seen whether future research directed at designing a test with high specificity for MH will show a lesser degree of positivity in patients with MMS.

Many of the clinical signs and laboratory abnormalities associated with MH occurred in our children during the perioperative period. None of the children with isolated MMS went on to develop fulminant MH. This was not the case in children with generalized rigidity, in whom the clinical picture was sufficiently convincing in four children to result in their being given dantrolene.

Early signs of anesthetic-induced MH reactions reported in the literature include increasing expired CO_2 tensions, tachycardia with or without ventricular extrasystoles and bigeminy, unstable increases in blood pressure, and deep, rapid respirations. Cyanosis and fever tend to occur late. Initial laboratory testing reveals evidence of increased metabolism, acidosis, and hyperkalemia. Somewhat later, myoglobinemia, myoglobinuria, and increase in CK levels develop (29).

One of the most consistent findings in metabolic disorders such as MH is an elevation in Pco_2. Volatile anesthetics are respiratory depressants, however, and in adults, $Paco_2$ levels during spontaneous ventilation with halothane anesthesia range from 40–60 mm Hg depending on a variety of factors, including end-tidal vapor concentration (30). Figures like these are not readily available in children undergoing anesthesia. This hinders the interpretation of hypercarbia. Most of the children in our isolated MMS group had Pco_2 values greater than 40 mm Hg (Table 4). In almost all the cases, a single intraoperative measurement of blood gas tensions was made. In the absence of $ETco_2$ monitoring, the trend in CO_2 level is impossible to determine and valuable information is lost. The present study highlights the need for follow-up sampling and consistency in the route (arterial, venous, or capillary) used to sample blood. In addition, the interpretation of pH and base deficit testing is difficult in the absence of established "normal" values for children who have fasted for up to 16 h. This is especially true in outpatients whose parents, despite instructions to the contrary, often offer the last oral intake at bedtime on the day preceding surgery.

Three additional laboratory tests have been used to assess the degree of rhabdomyolysis that occurs in MH, yet elevated serum levels of CK (31), myoglobinemia (32), and myoglobinuria (33) have been observed after uneventful anesthetics in pediatric patients in whom intravenous succinylcholine was used. These biochemical signs of muscle injury are enhanced when succinylcholine is administered in the presence of halothane (31,34).

Modest elevations in CK levels would be expected in our children, given the anesthetic induction technique used. Despite this, some of the values observed were quite high. This has been reported previously in halothane-succinylcholine–induced masseter spasm (2,3). Not surprisingly, children developing generalized rigidity had higher 18–24-h CK levels than children with isolated MMS (Table 6). Increases in this enzyme tended to be more pronounced in younger children at the intraoperative sampling point and in older children on the first postoperative day. Many explanations for this sequencing are possible, albeit speculative. Older children had postoperative intramuscular injections twice as often (15 vs 7) as younger children to treat pain or vomiting, an intervention likely to be repeated on more than one occasion in the first 24 h given the predominant inpatient status of the older children. However, because the number of factors possibly influencing CK levels (i.e., muscle mass, physical activity, race, age, sex) is large (35,36), the variables are confounding.

In the present study, serum and urine myoglobin concentrations were reported as either positive or not done owing to the lack of quantification in some of the earlier detection methods used. A positive urine test would imply that the serum myoglobin level was elevated. Our results are in keeping with the 40% occurrence of myoglobinemia reported by Ryan et al. (32). It is the degree of elevation in serum myoglobin that is important, because a pathologic threshold for rhabdomyolytic renal damage exists. Presence or absence of muscle fasciculations does not correlate with serum myoglobin levels (37), yet the prophylactic administration of defasciculating doses (0.05 mg/kg) of *d*-tubocurarine significantly reduces the degree of myoglobinemia/myoglobinuria observed in children, including those as young as 2 yr (36,37). Certainly, myoglobinuria is a common postoperative finding when the combination of halothane and succinylcholine is used. It would seem reasonable to adopt a routine practice of precurarization along with mechanisms to ensure adequate postoperative hydration and diuresis to prevent rhabdomyolytic renal damage. In certain instances, follow-up renal function studies may be indicated.

Recommendations regarding the clinical management of patients who develop MMS currently come in two forms: for example, Gronert recommends that the anesthetic be continued with nontriggering agents, while monitoring $ETco_2$, blood gas tensions, vital signs, and muscle tone (5). If changes occur suggesting an abnormal metabolic response, the case should be canceled and treatment begun with dantrolene. Rosenberg, on the other hand, recommends that anesthesia be discontinued (with or without dantrolene), surgery rescheduled, and the patient evaluated by muscle biopsy (6). We have reported on the outcome of an alternative anesthetic practice in cases of isolated MMS after administration of intravenous succinylcholine. In review of our data, presupposing a thorough preanesthetic evaluation and careful monitoring in an atmosphere where dantrolene and experienced assistants are readily available, we have modified our current practice of continuing the same anesthetic so that we now include continuous $ETco_2$ monitoring or serial determination of intraoperative blood gas tensions (in the absence of $ETco_2$) and serum (not urine) myoglobin testing. We continue the anesthetic with the knowledge that there is no increase in long-term anesthetic morbidity associated with the development of isolated MMS as compared with outcome data for the entire pediatric surgical population at this institution (12).

Masseter muscle spasm is a conundrum that is difficult to comprehend given the present level of understanding regarding its significance. Further characterization of this entity is needed to develop standardized criteria for diagnosis and to establish guidelines for management. Therefore, we agree with other centers at this time and advocate follow-up neurologic examination, serial resting CK determinations, and muscle biopsy testing to accumulate more data.

In summary, we found that MMS during anesthesia was not an uncommon event; it occurred at our institution over a 10-yr period in 0.3% of children who received intravenous succinylcholine in combination with a volatile agent. Some of the patients developed ventricular arrhythmias, hypercarbia, myoglobinuria, and increases in CK levels. Despite these clinical and laboratory abnormalities, all of the children had an uneventful postoperative recovery. We believe that anesthesia can be continued safely in cases of isolated MMS when careful monitoring accompanies diagnostic evaluation.

We are indebted to Dr. Douglas Craig and Dr. Robert Hudson for their editorial advice, to Mary Cheang of the Department of Biostatistics for statistical analysis of the data, to Dr. Marsha Cohen for providing the Follow-up Program data, and to Joanne Thom for her assistance in preparing the manuscript.

References

1. Gronert GA. Trismus: masseter spasm—when is it MH? Literature scan: Anesthesiology 1987;1:2,20.
2. Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. Anesth Analg 1986;65:161–4.
3. Flewellen EH, Nelson TE. Halothane-succinylcholine induced masseter spasm: indicative of malignant hyperthermia susceptibility? Anesth Analg 1984;63:693–7.
4. Donlon JV, Newfield P, Sreter F, Ryan JF. Implications of masseter spasm after succinylcholine. Anesthesiology 1978;49: 298–301.
5. Gronert GA. Management of patients in whom trismus occurs following succinylcholine. Anesthesiology 1988;68:653–4.
6. Rosenberg H. Management of patients in whom trismus occurs following succinylcholine. Anesthesiology 1988;68:654–5.
7. Flewellen EH, Nelson TE. Masseter spasm induced by succinylcholine in children: contracture testing for malignant hyperthermia: report of six cases. Can Anaesth Soc J 1982;29: 42–9.
8. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effect of succinylcholine on mouth opening. Anesthesiology 1987;67:459–65.
9. Fletcher JE, Rosenberg H. In vitro interaction between halothane and succinylcholine in human skeletal muscle: implications for malignant hyperthermia and masseter muscle rigidity. Anesthesiology 1985;63:190–4.
10. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: incidence and implications. Anesthesiology 1984; 61:772–5.
11. Carroll JB. Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. Anesthesiology 1987;67:559–61.
12. Cohen M, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. Anesth Analg 1990;70:160–7.
13. Berry FA, Lynch C. Succinylcholine and trismus. Anesthesiology 1989;70:161–2.
14. Cook DR, Fischer CG. Neuromuscular blocking effects of succinylcholine in infants and children. Anesthesiology 1975; 42:662–5.

15. Meakin G, Baker RD, McKiernan EP. Dose-response curves for suxamethonium in neonates, infants and children. Br J Anaesth 1988;61:105.
16. Smith CE, Donati F, Bevan DR. Dose-response curves for succinylcholine: single versus cumulative techniques. Anesthesiology 1988;69:338–42.
17. Meakin G. Underdosage with succinylcholine may lead to incorrect diagnosis of masseter spasm in children. Anesthesiology 1988;69:1025–6.
18. Saddler JM, Bevan JC, Plumley MH, Polomento RC, Donati F, Bevan DR. Jaw muscle tension after succinylcholine in children undergoing strabismus surgery. Can J Anaesth 1990;37:21–5.
19. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. Increased masticatory muscle stiffness during limb muscle flaccidity associated with succinylcholine administration. Anesthesiology 1988;69:11–6.
20. Rosenberg H. Trismus is not trivial. Anesthesiology 1987;67:453–5.
21. Lerman J. Controversies in pediatric anesthesia. Can J Anaesth 1988;35:S18–22.
22. Ording H. Incidence of malignant hyperthermia in Denmark. Anesth Analg 1985;64:700–5.
23. Fletcher JE, Rosenberg H. In vitro muscle contractures induced by halothane and suxamethonium. Br J Anaesth 1986;58:1433–9.
24. Heiman-Patterson TD, Rosenberg H, Fletcher JE, Tahmoush AF. Halothane-caffeine contracture testing in neuromuscular diseases. Muscle Nerve 1988;11:453–7.
25. Gronert GA. Controversies in malignant hyperthermia. Anesthesiology 1983;59:273–4.
26. Christian AS, Ellis FR, Halsall J. Is there a relationship between masseteric muscle spasm and malignant hyperthermia? Br J Anaesth 1989;62:540–4.
27. The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. Br J Anaesth 1984;56:1267–9.
28. Green Larach M. Standardization of the caffeine halothane muscle contracture test. Anesth Analg 1989;69:511–5.
29. Britt BA. Malignant hyperthermia. Can Anaesth Soc J 1985;32:666–77.
30. Eger EI II. Isoflurane: a review. Anesthesiology 1981;55:559.
31. Innes RK, Stromme JH. Rise in serum creatinine phosphokinase associated with agents in anaesthesia. Br J Anaesth 1973;45:185–90.
32. Ryan JF, Kagen LJ, Hyman AI. Myoglobinemia after a single dose of succinylcholine. N Engl J Med 1971;285:824–7.
33. Plötz J. Succinylcholine in children. Anesth Analg 1988;67:801.
34. Airaksinen MM, Tammisto T. Myoglobinuria after intermittent administration of succinylcholine during halothane anesthesia. Clin Pharmacol Ther 1965;7:583–7.
35. Passos MR, Gonzalez CH, Zatz M. Creatine-kinase and pyruvate-kinase activities in normal children. Am J Med Genetics 1985;22:255–62.
36. Cozanitis DA, Erkola O, Klemola U, Makela V. Precurarization in infants and children less than three years of age. Can J Anaesth 1987;34:17–20.
37. Blanc VF, Vaillancourt GV, Brisson G. Succinylcholine, fasciculations and myoglobinemia. Can Anaesth Soc J 1986;33:178–84.

ANESTH ANALG
1991;72:161–8

Cerebral Blood Flow Decreases With Time Whereas Cerebral Oxygen Consumption Remains Stable During Hypothermic Cardiopulmonary Bypass in Humans

Donald S. Prough, MD, Anne T. Rogers, MBChB, FRCP(C), David A. Stump, PhD, Raymond C. Roy, MD, PhD, A. Robert Cordell, MD, Julia Phipps, RN, and Carol L. Taylor, MAS

PROUGH DS, ROGERS AT, STUMP DA, ROY RC, CORDELL AR, PHIPPS J, TAYLOR CL. Cerebral blood flow decreases with time whereas cerebral oxygen consumption remains stable during hypothermic cardiopulmonary bypass in humans. Anesth Analg 1991;72:161–8.

Recent investigations demonstrate that cerebral blood flow (CBF) progressively declines during hypothermic, nonpulsatile cardiopulmonary bypass (CPB). If CBF declines because of brain cooling, the cerebral metabolic rate for oxygen ($CMRO_2$) *should decline in parallel with the reduction in CBF. Therefore we studied the response of CBF, the cerebral arteriovenous oxygen content difference* ($A - VD_{cere}O_2$)*, and* $CMRO_2$ *as a function of the duration of CPB in humans. To do this, we compared the cerebrovascular response to changes in the* $PaCO_2$*. Because sequential CBF measurements using xenon 133* (^{133}Xe) *clearance must be separated by 15–25 min, we hypothesized that a time-dependent decline in CBF would accentuate the CBF reduction caused by a decrease in* $PaCO_2$*, but would blunt the CBF increase associated with a rise in* $PaCO_2$*. We measured CBF in 25 patients and calculated the cerebral arteriovenous oxygen content difference using radial arterial and jugular venous bulb blood samples. Patients were randomly assigned to management within either a lower (32–48 mm Hg) or higher (50–71 mm Hg) range of* $PaCO_2$ *uncorrected for temperature. Each patient underwent two randomly ordered sets of measurements, one at a lower* $PaCO_2$ *and the other at a higher* $PaCO_2$ *within the respective ranges. Cerebrovascular responsiveness to changes in* $PaCO_2$ *was calculated as specific reactivity (SR), the change in CBF divided by the change in* $PaCO_2$*, expressed in* $mL \cdot 100\ g^{-1} \cdot min^{-1} \cdot mm\ Hg^{-1}$*. In the entire group of 25 subjects, SR was* $0.69 \pm 0.33\ mL \cdot 100\ g^{-1} \cdot min^{-1} \cdot mm\ Hg^{-1}$ *(SD) if* $PaCO_2$ *was reduced and* $0.10 \pm 0.30\ mL \cdot 100\ g^{-1} \cdot min^{-1} \cdot mm\ Hg^{-1}$ *if* $PaCO_2$ *was increased* ($P < 0.001$)*. In patients managed within the lower range of* $PaCO_2$*, SR was* 0.63 ± 0.31 *and* 0.21 ± 0.17*, respectively, when* $PaCO_2$ *was reduced or increased* ($P < 0.05$)*. In patients managed within the higher range of* $PaCO_2$*, SR was* 0.76 ± 0.38 *and* -0.01 ± 0.36*, respectively, when* $PaCO_2$ *was reduced or increased* ($P < 0.01$)*. Estimated* $CMRO_2$ *remained constant within groups from the initial to the repeat measurements. These results confirm a significant time-dependent decline of CBF during CPB. Moreover, by demonstrating that* $CMRO_2$ *did not change significantly as* $PaCO_2$ *was altered in either direction, they suggest that the CBF reduction cannot be attributed to progressive brain cooling during stable, hypothermic, nonpulsatile CPB, but must result from an alteration in cerebrovascular resistance.*

Key Words: BRAIN, OXYGEN CONSUMPTION—blood flow. HYPOTHERMIA, INDUCED. MEASUREMENT TECHNIQUES, CEREBRAL BLOOD FLOW. SURGERY, CARDIAC.

After cardiac surgery involving cardiopulmonary bypass (CPB), the incidence of transient and persistent neurologic and neuropsychologic complications exceeds 50% (1,2). Consequently, investigators have intensively studied the pathogenesis of postoperative neurologic injury and have examined potential methods for prevention of cerebral injury (3–7). Recent investigations have defined various aspects of cerebral circulatory physiology and pharmacology during hypothermic, nonpulsatile CPB (8–16) including the effects of temperature (8), $PaCO_2$ (8–11), PaO_2 (12), perfusion pressure (11,13,14), and the administration of thiopental and isoflurane (15).

In the course of an investigation of cerebral auto-

Supported in part by grant HL-33869 from the National Heart Lung and Blood Institute of the National Institutes of Health.

Presented in part at the 1989 annual meeting of the International Anesthesia Research Society, Orlando, Florida, March 4–8, 1989.

Received from the Departments of Anesthesia, Neurology, Cardiothoracic Surgery, and Public Health Sciences, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. Accepted for publication September 7, 1990.

Address correspondence to Dr. Prough, Section on Critical Care, Department of Anesthesia, Bowman Gray School of Medicine, Wake Forest University, 300 South Hawthorne Road, Winston-Salem, NC 27103

©1991 by the International Anesthesia Research Society

egulation, Rogers et al. reported the unexpected observation that cerebral blood flow (CBF) apparently declines during stable, hypothermic CPB (13). This ime effect was demonstrated in 12 patients who had CBF measured by xenon 133 (^{133}Xe) clearance at two ntervals, while systemic temperature, $Paco_2$, pump low (Q), hematocrit (Hct), and mean arterial pres- ure (MAP) were held constant. If CBF declines when MAP is held constant, then cerebrovascular resis- ance (CVR) is increasing, according to the equation:

$$\mathrm{CBF} = \frac{\mathrm{MAP} - \mathrm{JVP}}{\mathrm{CVR}},$$

where JVP is jugular venous pressure. One potential mechanism for a CBF decline and a CVR increase is progressive brain cooling and a progressive reduction n the cerebral metabolic rate for oxygen ($CMRo_2$) despite stable systemic temperatures. Alternatively, CVR may increase for reasons unrelated to changes in $CMRo_2$. Further characterization of the changes in CBF and $CMRo_2$ that occur as a function of the duration of CPB would provide information that ould be used to generate new hypotheses. For nstance, if $CMRo_2$ were to remain constant as CBF declined, other potential causes for changes in CVR would require further study.

Therefore, we investigated the effects of the dura- ion of CPB on cerebral vascular responsiveness to hanges in $Paco_2$. In patients undergoing CPB, CVR varies inversely with $Paco_2$ whereas CBF varies di- ectly (9). Cerebral vascular responsiveness to hanges in $Paco_2$ is expressed traditionally in terms of specific reactivity (SR):

$$\mathrm{SR} = \frac{\Delta \mathrm{CBF}}{\Delta Paco_2}, \tag{1}$$

where SR is expressed as mL·100 g^{-1}·min^{-1}·mm Hg^{-1} change in $Paco_2$. Cerebral vascular reactivity to hanges in $Paco_2$ is preserved during hypothermic CPB (8–11,16). However, measurements of CBF using ^{33}Xe during hypothermic CPB must be separated by t least 15–25 min. Therefore, we hypothesized that alculated SR would be greater if $Paco_2$ were reduced han if it were increased during hypothermic CPB, .e., the decline in CBF due to the time interval on CPB between measurements would accentuate the decline in CBF produced by a reduction in $Paco_2$. Conversely, the time-related decline in CBF would blunt the expected increase in CBF produced by an ncrease in $Paco_2$. By comparing cerebrovascular re- ctivity in patients having an increase versus having decrease in $Paco_2$, we hoped to further define any nfluence of the duration of CPB. Additionally, by haracterizing the response of $CMRo_2$ to these manipulations, we indirectly investigated one possible mechanism, i.e., progressive brain cooling.

Methods

The study was approved by the institutional Clinical Research Practices Committee, and each patient gave written informed consent. Twenty-five patients, scheduled for myocardial revascularization and free of clinical evidence of cerebrovascular disease or hypertension, were screened using carotid Doppler ultrasound to exclude asymptomatic extracranial cerebrovascular occlusive disease. After premedication with 2–4 mg/kg of oral lorazepam and 0.1 mg/kg IM morphine, patients were anesthetized with 75 μg/kg fentanyl, paralyzed with nondepolarizing muscle relaxants (pancuronium, metocurine, or a combination thereof), and mechanically ventilated with oxygen (O_2) to maintain normocarbia. Before initiating CPB, patients received 3–4 mg/kg IV heparin; additional doses, given as necessary, maintained an activated clotting time of greater than 400 s. No other drugs were given until the study measurements were completed; any patient requiring additional drugs for clinical reasons was excluded.

In all subjects, nonpulsatile hypothermic CPB was conducted using a membrane oxygenator, arterial line filter, and blood-free priming solution. Patients received two determinations of CBF and cerebral arteriovenous O_2 content difference ($A - VD_{cere}O_2$), after random assignment to one of two groups: in group 1 patients ($n = 13$), $Paco_2$ was maintained within a range of 32–48 mm Hg; in group 2 patients ($n = 12$), $Paco_2$ was maintained within a range of 50–71 mm Hg. The lower range is comparable to the strategy of $Paco_2$ management referred to as α-stat in the CPB literature; the upper range is comparable to pH-stat management (17). Within each group, patients were further assigned to $Paco_2$ manipulation in one of two randomly determined orders. In group 1A, $Paco_2$ was maintained initially at approximately 44 mm Hg (uncorrected for body temperature), then decreased to approximately 36 mm Hg ($n = 7$). In group 1B patients, the same sequence was reversed ($n = 6$). In group 2A ($n = 6$), $Paco_2$ was initially maintained at 65 mm Hg, then reduced to approximately 55 mm Hg. In group 2B ($n = 6$), the order was reversed. In each individual patient during both measurement intervals, MAP, Q, nasopharyngeal temperature (NPT), $Paco_2$, and Hct were maintained within 5% of the values determined during the first measurement interval. An in-line blood gas analyzer (Bentley Gas-Stat, CDI, Inc., Irvine, Calif.) monitored pH, CO_2, and PaCO_2 continuously during CPB, and these values were confirmed by intermittent arterial blood gas sampling.

Measurements of CBF, arterial oxygen content (CaO_2), jugular venous bulb O_2 content ($C_{jv}O_2$), and CMRO_2 calculations commenced after aortic cross-clamping when NPT had been stable for at least 5 min. Determination of CBF proceeded by injection of 3–5 mCi of ^{133}Xe dissolved in saline into the arterial inflow cannula of the pump oxygenator. Sixteen cadmium telluride gamma detectors measured gamma emissions, and a portable Micro Vax computer analyzed the ^{133}Xe clearance curves. Data from all 16 detectors were averaged to obtain mean global CBF for each patient at each measurement interval.

Cerebral venous effluent was sampled for measurement of O_2 tension ($P_{jv}O_2$) and of saturation ($S_{jv}O_2$) from a 20-gauge, 15-cm jugular bulb catheter inserted percutaneously and advanced in a retrograde direction from the right internal jugular vein. Blood samples were analyzed at 37°C in a blood gas analyzer (IL 813, Instrumentation Laboratory, Lexington, Mass.) and a CO-Oximeter (IL 282, same manufacturer). The $A - VD_{cere}O_2$ was calculated using systemic arterial and cerebral venous values for oxygen content, according to the standard formula

$$C_xO_2 = P_xO_2 \times 0.0031 + S_xO_2 \times Hgb \times 1.34, \tag{2}$$

where C_xO_2 is arterial or jugular venous bulb O_2 content, P_xO_2 is arterial or jugular venous bulb O_2 tension, uncorrected for body temperature, and S_xO_2 is O_2 saturation (measured in a CO-Oximeter at 37°C). We estimated CMRO_2 as the product of mean global CBF and $A - VD_{cere}O_2$. This estimate necessitates the assumption that CBF, measured primarily in cortical structures, is representative of whole-brain CBF and can therefore be multiplied by the whole-brain estimate of O_2 extraction.

After protocol adjustment of the PaCO_2 level, the second set of CBF and $A - VD_{cere}O_2$ measurements was completed. Each patient was monitored for recirculation of isotope and the amount of residual ^{133}Xe remaining after the first injection by means of a cadmium telluride detector applied to the arterial inflow tubing of the pump oxygenator. Recirculation was not detected in any case. To minimize artifact from residual background ^{133}Xe after the initial injection, we allowed at least 15 min to elapse between the first and second injections. As previously described (13,18), this ensures that the background radiation count is less than 2.5% of the peak count rate. The effect of any remaining ^{133}Xe was further minimized by increasing the ^{133}Xe dose by 50% for the second CBF determination. Analysis of the ^{133}Xe clearance curves was accomplished by the CBF_{15} method (18) developed by Obrist and Wilkinson (19). This noncompartmental analysis correlates well in CPB patients (18) with the height/area method, the reference standard for calculation of regional CBF by ^{133}Xe washout by direct intraarterial (internal carotid artery) injection. Injection of the radioisotope into the arterial inflow tubing results in distribution of a small proportion of tracer to the extracerebral tissues. However, the CBF_{15} computation integrates the clearance curve to 15 min only, eliminating the tail of the desaturation curve, thus diminishing the influence of the extracerebral compartment as a source of error. Accordingly, as suggested by several authors (19,20), we did not correct the ^{133}Xe clearance curves for extracerebral delivery and washout. The tissue-blood partition coefficient for xenon was corrected for decreases in temperature and hematocrit according to the formulas of Chen et al. (21).

The initial baseline and repeat CBF and $A - VD_{cere}O_2$ measurements in each group were averaged to obtain the mean ± SD for each group at each measurement interval. Cerebral blood flow data were employed to calculate SR in each patient as PaCO_2 either decreased or increased. Those calculations were as follows:

$$SR = \frac{\Delta CBF}{\Delta PaCO_2}. \tag{3}$$

The effect of the duration of CPB, termed time reactivity (TR), was calculated for each individual patient as follows:

$$TR = \frac{(SR_{mean} - SR_{ind}) \times \Delta PaCO_2}{t}, \tag{4}$$

where SR_{mean} is the average SR for all patients, SR_{ind} is the specific CO_2 reactivity for each patient, and t is the time interval between measurements in that patient. The average TR ± SD was then calculated.

Statistical Analysis

All values are expressed as mean ± SD. Controlled variables (MAP, Q, NPT, PaCO_2, and Hct) were calculated for descriptive purposes and for excluding differences at baseline using the Kruskal–Wallis test. Multivariate repeated measures analysis of variance was initially performed to determine whether the order of measurement (higher followed by lower or vice versa) exerted an important effect on the three primary dependent variables, CBF, $A - VD_{cere}O_2$, and CMRO_2. The factors considered in the three-way analysis included group, order of determination, and

Table 1. Controlled Variables (mean ± SD)

Group No. (direction of Paco$_2$ change)	Paco$_2$[a] (mm Hg)	Pao$_2$[a] (mm Hg)	MAP (mm Hg)	NPT (°C)	Q (L·min^{-1}·m^{-2})	Hct (vol %)
1A (decreasing)	44.3 ± 2.3	225 ± 57	69.4 ± 4.5	27.5 ± 0.7	2.0 ± 0.4	23.3 ± 3.0
	36.4 ± 2.4	238 ± 414	74.2 ± 5.5	27.6 ± 0.5	2.0 ± 0.3	23.5 ± 3.8
1B (increasing)	36.1 ± 2.3	256 ± 66	65.0 ± 11.6	27.1 ± 0.3	1.7 ± 0.4	23.0 ± 1.9
	45.6 ± 1.6	252 ± 104	68.5 ± 14.8	27.0 ± 0.4	1.7 ± 0.3	23.6 ± 2.3
2A (decreasing)	67.9 ± 2.3	257 ± 91	66.7 ± 7.7	27.0 ± 0.8	1.9 ± 0.4	25.3 ± 4.3
	55.6 ± 2.7	246 ± 61	70.3 ± 6.9	27.3 ± 0.8	1.9 ± 0.4	25.3 ± 4.5
2B (increasing)	54.9 ± 3.7	275 ± 149	68.2 ± 8.9	27.9 ± 0.6	1.9 ± 0.3	26.0 ± 3.7
	68.6 ± 1.8	246 ± 27	68.8 ± 8.3	28.1 ± 0.6	1.9 ± 0.3	26.0 ± 3.9

Paco$_2$, arterial carbon dioxide pressure; Pao$_2$, arterial oxygen pressure; MAP, mean arterial pressure; NPT, nasopharyngeal temperature; Q, pump flow; HCT, hematocrit.

[a] Uncorrected for patient temperature.

Table 2. Paco$_2$ and Dependent Variables (mean ± SD)

Group No. (direction of Paco$_2$ change)	Paco$_2$ (mm Hg)	CBF (mL·100 g^{-1}·min^{-1})	S$_{jv}$o$_2$ (% Sat)	A − VD$_{cere}$o$_2$ (mL/100 mL)	CMRo$_2$ (mL·100 g^{-1}·min^{-1})
1A (decreasing)	44.3 ± 2.3	15.6 ± 4.1	74.6 ± 6.1	3.1 ± 1.0	0.5 ± 0.1
	36.4 ± 2.4	11.0 ± 2.9[a]	63.6 ± 7.1	4.3 ± 1.1	0.5 ± 0.1
1B (increasing)	36.1 ± 2.3	12.3 ± 2.6	76.7 ± 9.5	2.8 ± 1.1	0.3 ± 0.2
	45.6 ± 1.6	14.3 ± 2.6	80.3 ± 11.2	2.4 ± 1.3	0.4 ± 0.1
2A (decreasing)	67.9 ± 2.3	31.8 ± 3.5	94.9 ± 3.4	0.7 ± 0.3	0.2 ± 0.1
	55.6 ± 2.7	22.6 ± 5.9[b]	91.7 ± 3.1	1.2 ± 0.3	0.3 ± 0.1
2B (increasing)	54.9 ± 3.7	27.6 ± 10.6	89.6 ± 6.7	1.5 ± 0.6	0.4 ± 0.1
	68.6 ± 1.8	26.9 ± 5.7	94.6 ± 3.5	0.8 ± 0.4	0.2 ± 0.1

Paco$_2$, arterial carbon dioxide pressure; CBF, cerebral blood flow; S$_{jv}$o$_2$, oxygen saturation; A − VD$_{cere}$o$_2$, cerebral arteriovenous oxygen content difference; CMRo$_2$, cerebral oxygen metabolic rate.

[a] $P < 0.05$ within group 1A.

[b] $P < 0.005$ within group 2A.

level of Paco$_2$ (higher and lower). When an interaction occurred among factors, a multivariate repeated measures analysis of variance was performed for each variable to define further the effects of the other variables. Where significant differences existed, Tukey's multiple comparison procedure was applied to determine at what interval these differences occurred (22). Differences in SR between groups were analyzed using analysis of variance. Statistical significance was inferred if $P < 0.05$.

Results

Table 1 demonstrates that the controlled variables Pao$_2$, MAP, NPT, Q, and Hct were comparable at both measurement intervals within groups 1A, 1B, 2A, and 2B; by experimental design, Paco$_2$ differed between the two intervals in each subgroup. The average time intervals between measurements were 25.9 ± 11.6 min in group 1A, 22.5 ± 4.8 min in group 1B, 21.8 ± 9.2 min in group 2A, and 22.3 ± 9.7 min in group 2B.

Table 2 shows the changes in the dependent variables, CBF, S$_{jv}$o$_2$, A − VD$_{cere}$o$_2$, and CMRo$_2$ in both groups. As predicted, the CBF response to changes in Paco$_2$ differed significantly between groups 1A and 1B and between groups 2A and 2B depending on the direction of CO$_2$ change (Table 3). A significant ($P = 0.02$) three-way interaction was present among group, level of Paco$_2$, and order of determination (i.e., higher Paco$_2$ followed by lower or lower followed by higher). There was a significant interaction between order and level of Paco$_2$ ($P < 0.05$ in both groups) and between order and group. When analysis of variance was performed within each order of determination, the change in CBF was *only* significant if the determination at the higher level of Paco$_2$ preceded the determination at the lower level of Paco$_2$ ($P < 0.05$ in group 1A and $P < 0.005$ in group 2A; Figure 1). The same is true if the data from both groups are combined (Figure 2). If CBF is plotted as a function of the interval between measurements, CBF values obtained at comparable levels of Paco$_2$ are lower if they are performed after a 15–25 min longer interval of hypothermic CPB. The effect is evident

Table 3. Effects of Changes in $Paco_2$ and Duration of CPB (mean ± SD)

Group No. (direction of $Paco_2$ change)	Time between measurements (min)	SR of CBF to CO_2 ($mL \cdot 100\ g^{-1} \cdot min^{-1} \cdot mm\ Hg^{-1}$)	TR: decline in CBF secondary to duration of CPB ($mL \cdot 100\ g^{-1} \cdot min^{-1} \cdot min^{-1}$)
1A (decreasing)	25.8 ± 11.6	0.63 ± 0.3	0.1 ± 0.1
1B (increasing)	21.4 ± 4.5	0.21 ± 0.2[a]	0.1 ± 0.1
2A (decreasing)	21.8 ± 9.2	0.76 ± 0.4	0.3 ± 0.1
2B (increasing)	22.3 ± 9.7	−0.01 ± 0.4[b]	0.4 ± 0.5

$Paco_2$, arterial carbon dioxide pressure; SR, specific reactivity; CBF, cerebral blood flow; TR, time reactivity; CPB, cardiopulmonary bypass.
[a] $P < 0.05$ within group 1.
[b] $P < 0.01$ within group 2.

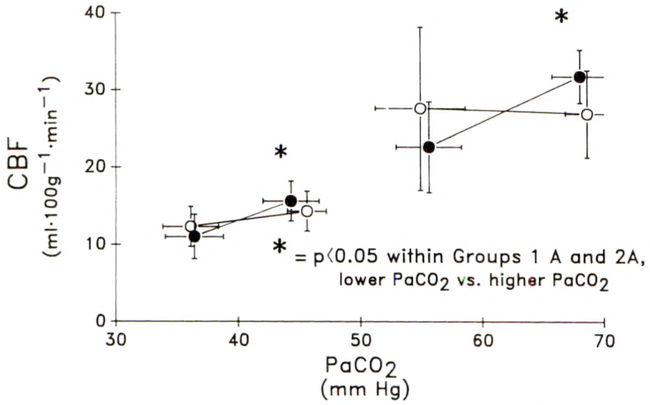


Figure 1. Relationship between CBF and $Paco_2$ in all patients in whom $Paco_2$ was reduced or increased. When $Paco_2$ was reduced (*closed circles*) either at a lower level of $Paco_2$ (group 1A) or at a higher level of $Paco_2$ (group 2A), the decrease in CBF was statistically significant. When $Paco_2$ was increased (*open circles*), no significant change in CBF occurred either at a lower level of $Paco_2$ (group 1B) or at a higher level (group 2B). These data suggest that a time-dependent decrease in CBF accentuated the decrease produced by a decrease in $Paco_2$ and blunted the increase associated with an increase in $Paco_2$.

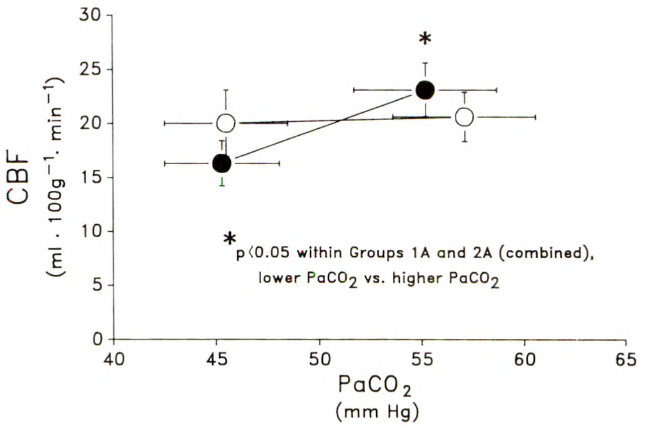


Figure 2. Relationship between CBF and $Paco_2$ in all patients in whom $Paco_2$ was reduced (*closed circles*; groups 1A and 2A combined) or increased (*open circles*; groups 1B and 2B combined). In the combined series, the decrease in CBF was statistically significant in the patients in whom $Paco_2$ was reduced. In contrast, CBF did not change if $Paco_2$ was increased. When the two groups are combined, the data suggest that a time-dependent decrease in CBF accentuated the decrease produced by a decrease in $Paco_2$ and blunted the increase associated with an increase in $Paco_2$.

both during α-stat management (Figure 3) and pH-stat management (Figure 4).

As CBF changed, $A - VD_{cere}o_2$ varied in a reciprocal fashion (Table 2). Therefore, $CMRo_2$ did not change significantly in any group between measurement intervals (Table 2). Analysis of variance performed within each order of determination demonstrated a significant group effect on $A - VD_{cere}o_2$. Within each group, the level of $Paco_2$ exerted a significant effect on $A - VD_{cere}o_2$ ($P < 0.05$ in group 1 and $P < 0.001$ in group 2). There were no three-way interactions among level of $Paco_2$, order of determination, and group, nor was there any effect of the order of determination alone on $CMRo_2$.

The TR, i.e., the decrement in CBF attributable to the duration of CPB, is displayed in Table 3. Each minute of hypothermic CPB resulted in a decrease of 0.1 ± 0.1 $mL \cdot 100\ g^{-1} \cdot min^{-1} \cdot min^{-1}$ in groups 1A and 1B and 0.3 ± 0.1 and 0.4 ± 0.5 $mL \cdot 100\ g^{-1} \cdot min^{-1} \cdot min^{-1}$ in groups 2A and 2B, respectively. Calculated as a percent of baseline CBF, these values approximate a decline of 1% per minute, a value comparable to that previously reported (13).

Discussion

By demonstrating that cerebrovascular responses to $Paco_2$ can be demonstrated during CPB only if $Paco_2$ is reduced, these data confirm the observation, first reported in humans by Rogers et al., that CBF declines spontaneously during stable, hypothermic CPB (13). The spontaneous decline is of sufficient magnitude that it completely obscures CBF changes secondary to increasing $Paco_2$. Not all investigators have reported similar findings. Govier et al., using stepwise linear regression analysis to correlate CBF with a variety of factors, found no apparent relationship

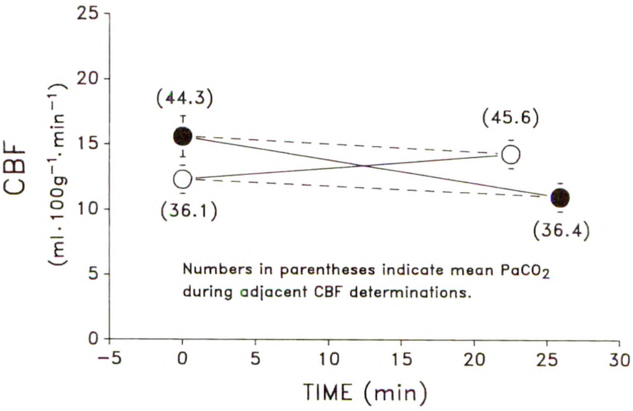


Figure 3. Relationship between CBF and the duration of CPB, in minutes, between first and second measurements of CBF in group 1 patients managed within the lower (α-stat) range of Paco$_2$. The *closed circles* represent patients in whom the first CBF was performed at a higher level of Paco$_2$ followed by a lower Paco$_2$ (group 1A). The mean higher and lower levels of Paco$_2$ are shown in parentheses adjacent to the appropriate symbol. Patients in whom the first measurement of CBF was performed at a lower level of Paco$_2$ followed by a higher level of Paco$_2$ are represented by the *open circles* (group 1B), accompanied by the corresponding mean levels of Paco$_2$ at each interval. The *dotted lines* represent a visual approximation of the change in CBF as a function of the duration of CPB.

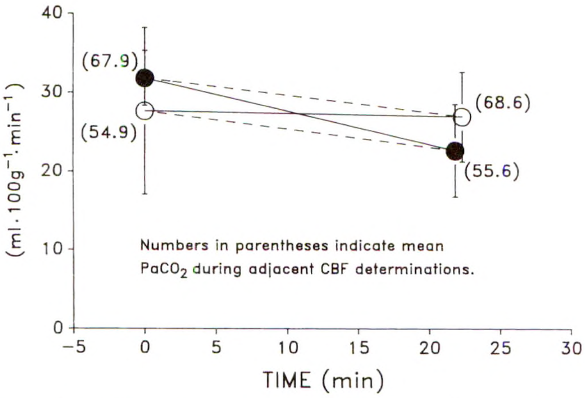


Figure 4. Relationship between CBF and the duration of CPB, in minutes, between first and second measurements of CBF in group 2 patients managed within the higher (pH-stat) range of Paco$_2$. The *closed circles* represent patients in whom the first CBF was performed at a higher level of Paco$_2$ followed by a lower Paco$_2$ (group 2A). The mean higher and lower levels of Paco$_2$ are shown in parentheses adjacent to the appropriate symbol. Patients in whom the first measurement of CBF was performed at a lower level of Paco$_2$ followed by a higher level of Paco$_2$ are represented by the *open circles* (group 2B), accompanied by the corresponding mean levels of Paco$_2$ in each group. The *dotted lines* represent a visual approximation of the change in CBF as a function of the duration of CPB.

between CBF and duration of CPB (8). The discrepancy between various studies may be explained by differences in experimental design and in statistical analysis. In the present study and that by Rogers et al., two sequential data points were obtained in each patient, while CPB conditions were maintained constant. In contrast, Govier et al. studied multiple data points in an extensive series of patients and subjected the results to factor analysis. Because of the profound effects of Paco$_2$ and temperature on CBF (8,9), subtle effects, such as those attributable to CPB duration, might be overshadowed in the latter type of analysis.

Of great importance is the demonstration that the observed time-dependent reduction in CBF during CPB apparently is not accompanied by a concomitant fall in CMRo$_2$. Therefore, we conclude that progressive brain cooling during stable hypothermic CPB does not explain the gradual decline in CBF. These data may suggest that the duration of CPB alters cerebrovascular reactivity such that CBF no longer responds appropriately to vasodilator stimuli. A similar conclusion is suggested by intriguing data, presented in preliminary form by Croughwell and colleagues, that demonstrate failure of CBF in some patients to increase proportionately to CMRo$_2$ increases during rewarming after hypothermic CPB (23). Alternatively, the decline in CBF at a constant MAP could be attributable to progressive vasoconstriction (from unidentified factors) or to microvascular obstruction (e.g., from accumulating embolic debris).

According to Shaw et al., the etiology of neurologic and neuropsychologic deficits following CPB is likely to be multifactorial (1), with potential mechanisms that include macroembolization or microembolization of particulate matter or air and global cerebral hypoperfusion. Although focal embolic phenomena are responsible for many post-CPB deficits (1,3,5,24,25), some data suggest that cerebral hypoperfusion secondary to incomplete global ischemia or cerebrovascular disease plays an important role in certain patients (4,26). If global cerebral hypoperfusion contributes to post-CPB brain injury, an understanding of factors that tend to reduce CBF in relation to cerebral O$_2$ consumption is essential to the development of strategies to limit neurologic injury.

The present study suggests that the ability of CBF to meet metabolic demand progressively declines during CPB. As the duration of CPB increases, CBF declines. This phenomenon is emphasized by the difference in jugular venous saturation at a Paco$_2$ of approximately 36 mm Hg in groups 1A and 1B (Table 2), i.e., 77% ± 10% at the lower level of Paco$_2$ if Paco$_2$ is increased ($P < 0.05$) as compared to 64% ± 7% at the lower level of Paco$_2$ if Paco$_2$ is reduced. Because CMRo$_2$ remains constant, cerebral O$_2$ extraction progressively increases as CBF falls. In the absence of a time effect, these S$_{jv}$o$_2$ values should have been similar. At normothermia, the normal P$_{jv}$o$_2$ is 40 mm

Hg ($S_{jv}o_2$ approximately 70%) (27). In this data set, one patient in group 1 had a reduction in $P_{jv}o_2$ to 28 mm Hg (temperature uncorrected) at a $Paco_2$ of 35 mm Hg, and four had values of $P_{jv}o_2$ below 34 mm Hg at $Paco_2$ values ranging from 33 to 37 mm Hg. Although none of the subjects in this study demonstrated gross neurologic deficits, detailed neuropsychologic testing to detect subtle deficits in psychomotor performance associated with CPB (1,2,7) was not performed.

Because all incidences of low jugular venous saturation occurred in patients managed at a lower level of $Paco_2$, these data are relevant to a continuing controversy regarding the management of $Paco_2$ during hypothermic CPB. Two levels of $Paco_2$, termed pH-stat and α-stat, are commonly used during hypothermic CPB (17). The pH-stat method, in which the temperature-corrected pH and $Paco_2$ are held near 7.40 and 40 mm Hg, respectively, requires that CO_2 be added to the gas entering the pump oxygenator so that, as measured at 37°C in the blood gas machine, the pH is lower than 7.40 and the $Paco_2$ is higher than 40 mm Hg. At 27°C body temperature, a temperature-corrected $Paco_2$ of 40 mm Hg corresponds to an uncorrected value of 60 mm Hg. In contrast, the α-stat method defines 7.40 and 40 mm Hg, measured at 37°C, as desirable goals. A considerable body of work suggests that the latter approach may be more physiologic, as inferred from acid-base alterations produced by temperature changes in poikilothermic animals (28–30). However, hibernating mammals (heterotherms) change pH as they cool in a manner more characteristic of the pH-stat form of management (31).

Bashein et al. have suggested recently that the choice of α-stat or pH-stat management does not alter postoperative neuropsychologic testing (7). Our data suggest that selection of α-stat acid-base management may be associated in some patients with substantially reduced CBF levels during hypothermic CPB, compensated for by increased O_2 extraction. Any further reduction in $Paco_2$, superimposed on the reduction in CBF occurring as a function of the duration of CPB, could potentially reduce CBF to a level at which metabolic demands are no longer adequately met.

Our investigation did not address the question of whether the reduction in CBF that occurs as a function of time poses a physiologic risk to the patient undergoing hypothermic CPB. Debate persists regarding the mechanism of the continued high incidence of adverse neuropsychiatric sequelae (1,2). Therefore, the clinical importance of the time-related decline requires further investigation. If multiple embolic phenomena account for post-CPB neurologic complications, then the time-related reduction in CBF relative to other organs could reduce the proportion of emboli reaching the cerebral circulation. If, in contrast, cerebral hypoperfusion explains the deficits, further reduction in flow as CPB continues could aggravate injury.

In summary, we have confirmed that CBF progressively declines during stable hypothermic CPB. Because $CMRo_2$ remains stable, O_2 extraction increases as CBF falls. Further studies should investigate the significance and application of these findings to postoperative neurologic deficits after cardiac surgery.

The authors gratefully acknowledge the invaluable contribution of David Charles, Chief Perfusionist, North Carolina Baptist Hospital. We also gratefully acknowledge the excellent secretarial assistance of Kim Barnes and the editorial assistance provided by Faith McLellan.

References

1. Shaw PJ, Bates D, Cartlidge NE, et al. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. Stroke 1987;18:700–7.
2. Harrison MJ, Schneidau A, Ho R, Smith PL, Newman S, Treasure T. Cerebrovascular disease and functional outcome after coronary artery bypass surgery. Stroke 1989;20:235–7.
3. Slogoff S, Girgis KZ, Keats AS. Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass. Anesth Analg 1982;61:903–11.
4. Gravlee GP, Hudspeth AS, Toole JF. Bilateral brachial paralysis from watershed infarction after coronary artery bypass. A report of two cases and review of the predisposing anatomic and physiological mechanisms. J Thorac Cardiovasc Surg 1984; 88:742–7.
5. Blauth CI, Arnold JV, Schulenberg WE, McCartney AC, Taylor KM, Loop FD. Cerebral microembolism during cardiopulmonary bypass. Retinal microvascular studies in vivo with fluorescein angiography. J Thorac Cardiovasc Surg 1988;95:668–76.
6. Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 1986;64:165–70.
7. Bashein G, Townes BD, Nessly ML, et al. A randomized study of carbon dioxide management during hypothermic cardiopulmonary bypass. Anesthesiology 1990;72:7–15.
8. Govier AV, Reves JG, McKay RD, et al. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. Ann Thorac Surg 1984;38:592–600.
9. Prough DS, Stump DA, Roy RC, et al. Response of cerebral blood flow to changes in carbon dioxide tension during hypothermic cardiopulmonary bypass. Anesthesiology 1986;64:576–81.
10. Prough DS, Rogers AT, Stump DA, Mills SA, Gravlee GP, Taylor C. Hypercarbia depresses cerebral oxygen consumption during cardiopulmonary bypass. Stroke 1990;21:1162–6.
11. Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of $Paco_2$. Anesth Analg 1987;66:825–32.

12. Rogers AT, Stump DA, Prough DS, Angert KC, Wallenhaupt SA. Cerebrovascular responsiveness to Pa_{O_2} is preserved during hypothermic cardiopulmonary bypass (abstract). Anesthesiology 1987;67:A12.

13. Rogers AT, Stump DA, Gravlee GP, et al. Response of cerebral blood flow to phenylephrine infusion during hypothermic cardiopulmonary bypass: influence of Pa_{CO_2} management. Anesthesiology 1988;69:547–51.

14. Rogers AT, Prough DS, Stump DA, et al. Cerebral blood flow does not change following sodium nitroprusside infusion during hypothermic cardiopulmonary bypass. Anesth Analg 1989;68:122–6.

15. Woodcock TE, Murkin JM, Farrar JK, Tweed WA, Guiraudon GM, McKenzie FN. Pharmacologic EEG suppression during cardiopulmonary bypass: cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and normothermia. Anesthesiology 1987;67:218–24.

16. Wollman H, Stephen GW, Clement AJ, Danielson GK. Cerebral blood flow in man during extracorporeal circulation. J Thorac Cardiovasc Surg 1966;52:558–64.

17. White FN, Weinstein Y. Carbon dioxide transport and acid-base balance during hypothermia. In: Utley JR, Betleski R, eds. Pathophysiology and techniques of cardiopulmonary bypass. Volume II. Baltimore: Williams & Wilkins, 1983:40–8.

18. Rogers AT, Stump DA, Prough DS, Hinshelwood L, Gravlee GP. Cerebral blood flow during hypothermic cardiopulmonary bypass by ^{133}Xe clearance: a comparison of computation methods (abstract). Anesthesiology 1988;69:A136.

19. Obrist WD, Wilkinson WE. Stability and sensitivity of CBF indices in the noninvasive ^{133}Xe method. In: Hartman A, Hoyer S, eds. Cerebral blood flow and metabolism measurement. New York: Springer Verlag, 1985:30–6.

20. Seylaz J, Meric P. Two-dimensional measurements of rCBF by the intravenous xenon method. In: Hartman A, Hoyer S, eds. Cerebral blood flow and metabolism measurement. New York: Springer Verlag, 1985:37–51.

21. Chen RY, Fan FC, Kim S, Jan KM, Usami S, Chien S. Tissue-blood partition coefficient for xenon: temperature and hematocrit dependence. J Appl Physiol 1980;49:178–83.

22. Montgomery DC. Design and analysis of experiments. New York: John Wiley & Sons, 1984:69.

23. Croughwell N, Newman M, Quill T, et al. Warming during cardiopulmonary bypass is associated with jugular bulb desaturation (abstract). Anesth Analg 1990;70:S72.

24. Fish KJ. Microembolization: etiology and prevention. In: Hilberman M, ed. Brain injury and protection during open-heart surgery. Boston: Martinus Nijhoff, 1988:67–83.

25. Nussmeier NA, McDermott JP. Macroembolization: prevention and outcome modification. In: Hilberman M, ed. Brain injury and protection during open-heart surgery. Boston: Martinus Nijhoff, 1988:85–107.

26. Malone M, Prior P, Scholtz CL. Brain damage after cardiopulmonary bypass: correlations between neurophysiological and neuropathological findings. J Neurol Neurosurg Psychiatry 1981;44:924–31.

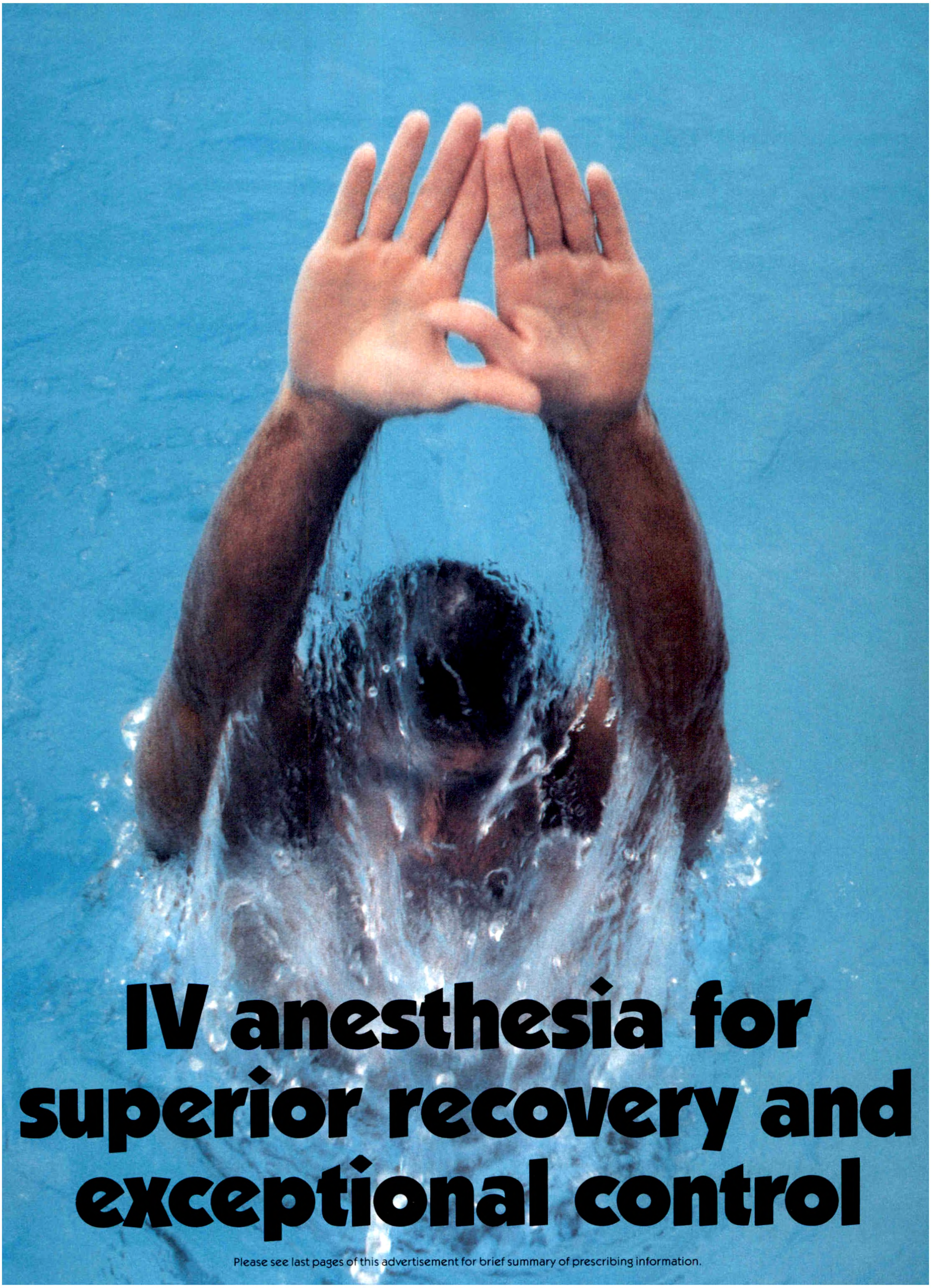
27. McDowall DG. Monitoring the brain. Anesthesiology 1976;45: 117–34.

28. White FN. A comparative physiologic approach to hypothermia. J Thorac Cardiovasc Surg 1981;82:821–31.

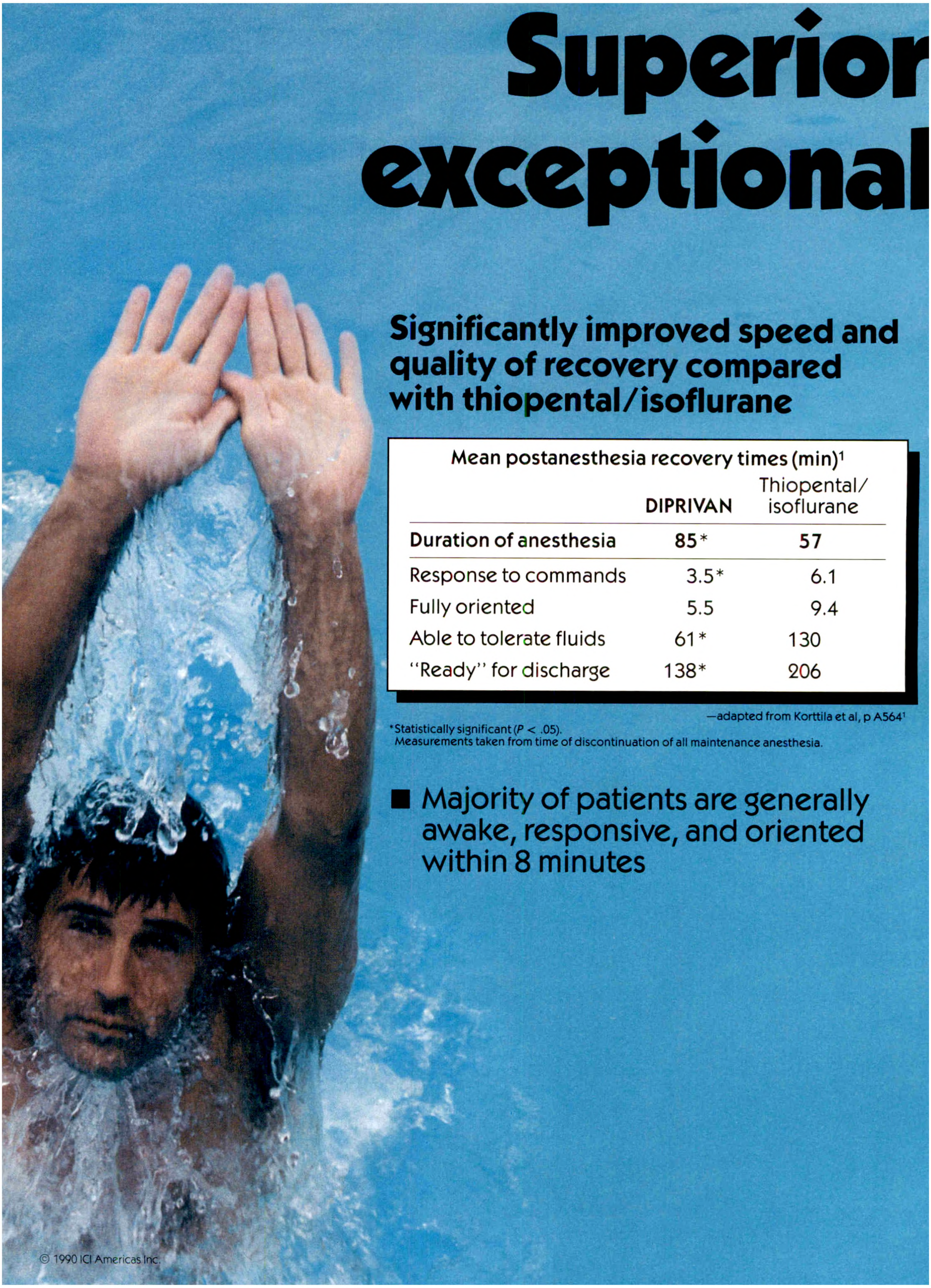
29. Williams JJ, Marshall BE. A fresh look at an old question. Anesthesiology 1982;56:1–2.

30. Rahn H, Reeves RB. Hydrogen ion regulation during hypothermia: from the Amazon to the operating room. In: Prakash O, ed. Applied physiology in clinical respiratory care. Boston: Martinus Nijhoff, 1982:1–15.

31. Wilson TL. Theoretical analysis of the effects of two pH regulation patterns on the temperature sensitivities of biological systems in nonhomeothermic animals. Arch Biochem Biophys 1977;182:409–19.



Please see last pages of this advertisement for brief summary of prescribing information.



Superior
exceptional

Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

© 1990 ICI Americas Inc.

ecover, and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

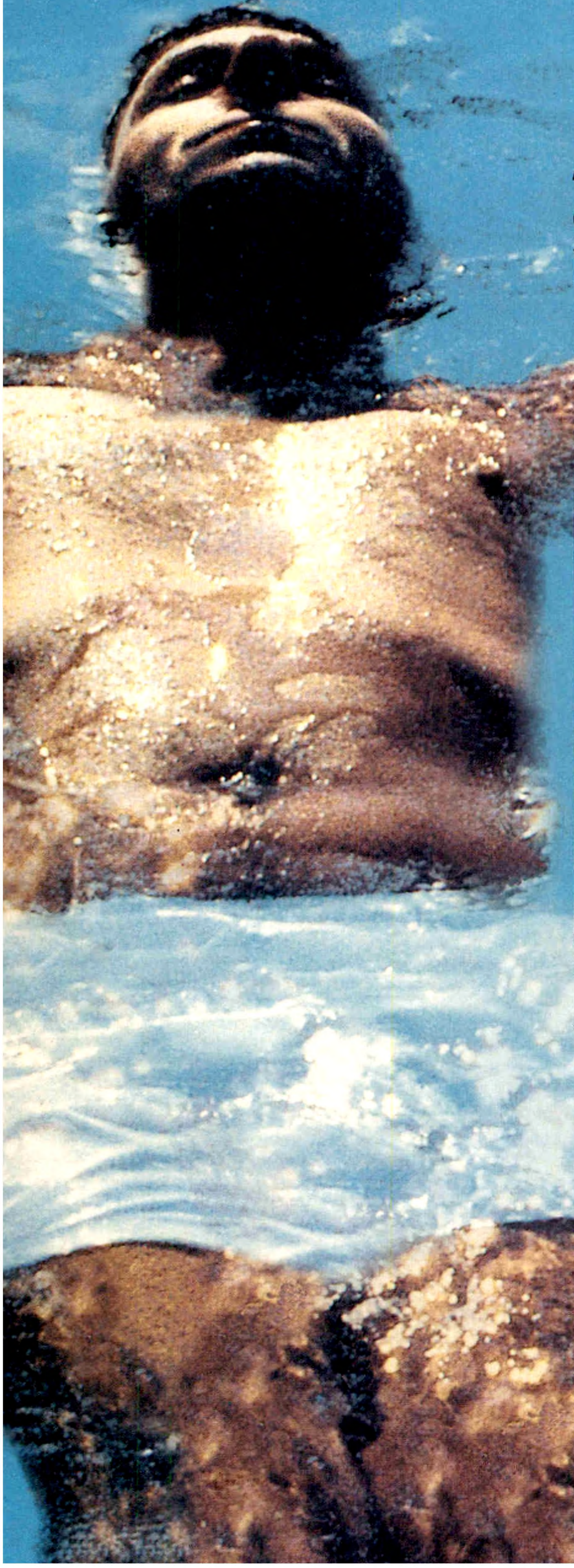
As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

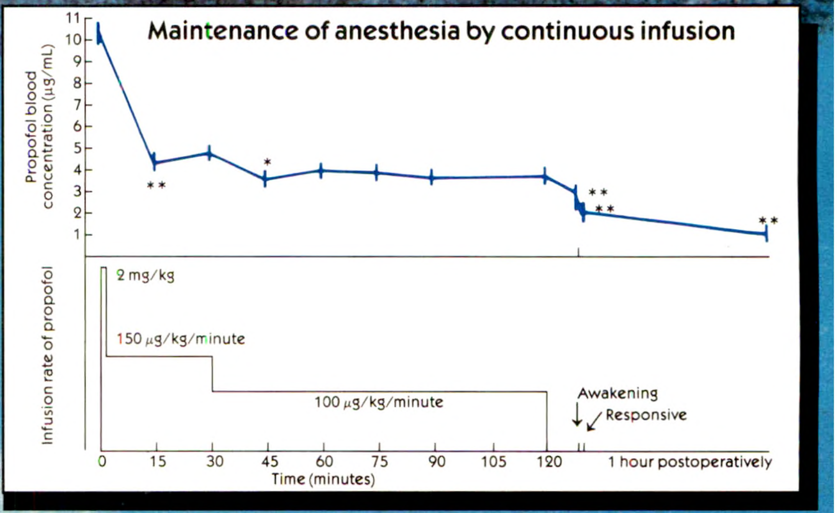
DIPRIVAN®
INJECTION propofol

Superior
exceptional



Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364[4]

*Significant difference ($P <$ .05) from previous value.
**$P <$ .02. (Mean and SEM values are shown.)
After a loading dose of 2 mg/kg, anesthesia was maintained with 150 μg/kg/min for 30 minutes—then 100 μg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

ecover[illegible], and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Since the vehicle (soybean oil in water emulsion) is capable of supporting rapid growth of microorganisms, strict aseptic technique must always be maintained while handling DIPRIVAN Injection. (See WARNINGS and DOSAGE AND ADMINISTRATION sections in the brief summary of prescribing information at the end of this advertisement.)

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.
[†] Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®
INJECTION
propofol

For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: 1. Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. 2. Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 3. Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. 4. Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. 5. Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

Please see last pages of this advertisement for brief summary of prescribing information.

STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

DIPRIVAN®

INJECTION
10 mg/mL
propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.)*

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

– 5% Dextrose Injection, USP
– Lactated Ringers Injection, USP
– Lactated Ringers and 5% Dextrose Injection
– 5% Dextrose and 0.45% Sodium Chloride Injection, USP
– 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should then commence without extended delay.

DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure.

Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness.

Rev. X 06/90

Made in Sweden
Manufactured for:
STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
65th CONGRESS — March 8–12, 1991
Marriott Rivercenter • San Antonio, Texas

MEETING REGISTRATION, HOTEL RESERVATION, SCIENTIFIC MEETING INFORMATION: Will be mailed in December to all IARS members. (IARS members outside of North America who plan to attend the meeting will receive this material by airmail upon request.) Non-IARS members should request information from the **NEW IARS OFFICE ADDRESS:** Suite 140, 2 Summit Park Drive, Cleveland, OH 44131. Tel: (216) 642-1124.

MEETING SCHEDULE: **Registration:** Friday, March 8, 1–6 PM
Scientific Program: Saturday–Tuesday, March 12
Exhibits: Saturday–Monday, March 11

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture, Sunday, March 10,
"Anesthesia Journals: The Backbone of the Specialty — Past, Present, and Future"
Nicholas M. Greene, MD, Emeritus Professor of Anesthesiology,
Yale University School of Medicine, New Haven, Connecticut,
and Editor-in-Chief, *ANESTHESIA and ANALGESIA*

REVIEW COURSE LECTURES:

MD Abel, MD — Transesophageal Echocardiography — Its Real Role in Clinical Anesthesia
PG Barash, MD — Preoperative Assessment of the Patient With Cardiac Disease
DR Bevan, MD, and RD Miller, MD — Anesthesia Literature — A Critical Approach to Reading and Writing
DR Cook, MD — Anesthetic Management of Neonatal and Infant Surgical Emergencies
MJ Cousins, MD — The Injury Response and the Prevention of Postoperative Pain
BG Covino, MD — New Techniques in Regional Anesthesia
N Ellison, MD — Blood Transfusions — When and What?
M Finster, MD — Newer Trends in Obstetric Pain Relief
AB Froese, MD — Ventilator-Related Lung Injury — New Concepts
TJ Gal, MD — Anesthesia and Gas Exchange — HPV, FRC, CC, and Other Acronyms
DE Longnecker, MD — The Case for Perioperative Blood Pressure Control
M Maze, MD — Alpha-2 Agonists and Anesthesia
SC Nicolson, MD — Perioperative Fluid Management in the Pediatric Patient
WS Nimmo, MD — Alternate Modes of Drug Delivery
GW Ostheimer, MD — Contemporary Issues in Obstetric Anesthesia
RG Pearl, MD — Sepsis — Etiology and Management
DS Prough, MD — Anesthetic Management of the Patient With Head Trauma
C Prys-Roberts, DM — Total Intravenous Anesthesia — Assessment of Adequacy
JG Reves, MD — Physiology of Cardiopulmonary Bypass
JJ Savarese, MD — Does the Choice of Muscle Relaxant Really Matter?
S Slogoff, MD — Outcome Studies in Anesthetic Data — A Perspective
NT Smith, MD — Perioperative Anesthetic Data — What to Do With It?
RK Stoelting, MD — Allergy and Anesthesia
JH Tinker, MD — How?/Should?/Does? Malpractice Litigation Affect Anesthetic Practice?
PF White, MD — Monitored Anesthesia Care — Appropriate Use of Adjuvant Drugs
MP Yeager, MD — The Role of Regional Anesthesia in Improving Surgical Outcome

PANELS

ANESTHESIA MACHINES AND VENTILATORS — Saturday, March 9, 8:00 AM
NW Lawson, MD, Moderator; JJ Andrews, MD, J Condurso, North American Drager, and JB Biondi, Ohmeda
YOU, THE ANESTHESIOLOGIST IN COURT — A MOCK MEDICAL MALPRACTICE TRIAL
(Based on an actual case) — Saturday, March 9, 1:00 PM
DH Morrow, MD, Moderator; Hon. D Hittner, F Stein, MD, TP Sartwelle, Esq., RJ Swift, Esq.
MEDICAL LITIGATION: PROBING THE DEPTHS — Sunday, March 10, 8:00 AM
PG Fine, MD, Moderator; AR Nelson, MD, JA Jacobson, MD, L Andrews, JD
LEGISLATIVE UPDATE — LUNCHEON SESSION — Sunday, March 10
BP Stephenson, MD, and AC Lang, representing American Society of Anesthesiologists
EMERGENCY AIRWAY MANAGEMENT — Monday, March 11, 8:00 AM
MS Gorback, MD, Moderator; JL Benumof, MD, EJ Krane, MD, CB Watson, MD

CLINICAL AND RESEARCH PRESENTATIONS

More than 300 clinical and research papers will be presented in concurrent oral and poster sessions.

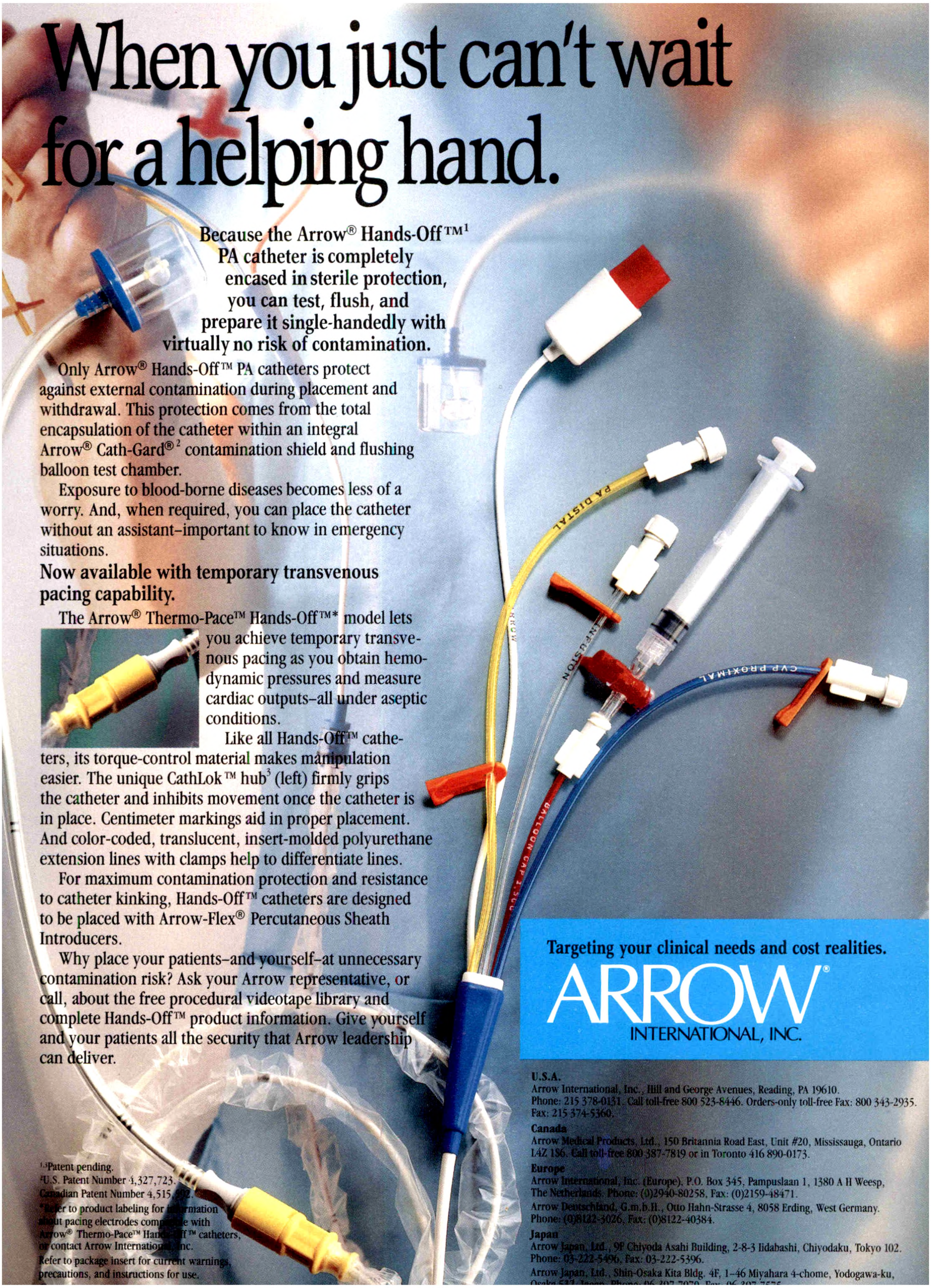
REGISTRATION • CME CREDIT • AIR TRAVEL • HOTELS

FEES: IARS Members — $275 ($300 on site) Non-members — $450 ($475 on site)
IARS Educational Members — No fee Non-member residents — $50 (with certification)

CME CREDIT: Category 1 — 27 hours

DELTA SPECIAL AIRFARES: Discounted fares for IARS meeting registrants. For details call 1-800-241-6760, File No. P-0095.

HOTELS: The Marriott Rivercenter will serve as headquarters hotel where all meetings and exhibits will be held. A limited number of additional rooms have been blocked at the St. Anthony. Reservation forms to be included in the December mailing must be used to obtain the discounted rates of IARS meeting registrants.



When you just can't wait for a helping hand.

Because the Arrow® Hands-Off™[1] PA catheter is completely encased in sterile protection, you can test, flush, and prepare it single-handedly with virtually no risk of contamination.

Only Arrow® Hands-Off™ PA catheters protect against external contamination during placement and withdrawal. This protection comes from the total encapsulation of the catheter within an integral Arrow® Cath-Gard®[2] contamination shield and flushing balloon test chamber.

Exposure to blood-borne diseases becomes less of a worry. And, when required, you can place the catheter without an assistant–important to know in emergency situations.

Now available with temporary transvenous pacing capability.

The Arrow® Thermo-Pace™ Hands-Off™* model lets you achieve temporary transvenous pacing as you obtain hemodynamic pressures and measure cardiac outputs–all under aseptic conditions.

Like all Hands-Off™ catheters, its torque-control material makes manipulation easier. The unique CathLok™ hub[3] (left) firmly grips the catheter and inhibits movement once the catheter is in place. Centimeter markings aid in proper placement. And color-coded, translucent, insert-molded polyurethane extension lines with clamps help to differentiate lines.

For maximum contamination protection and resistance to catheter kinking, Hands-Off™ catheters are designed to be placed with Arrow-Flex® Percutaneous Sheath Introducers.

Why place your patients–and yourself–at unnecessary contamination risk? Ask your Arrow representative, or call, about the free procedural videotape library and complete Hands-Off™ product information. Give yourself and your patients all the security that Arrow leadership can deliver.

Targeting your clinical needs and cost realities.

ARROW®
INTERNATIONAL, INC.

U.S.A.
Arrow International, Inc., Hill and George Avenues, Reading, PA 19610.
Phone: 215 378-0131. Call toll-free 800 523-8446. Orders-only toll-free Fax: 800 343-2935.
Fax: 215 374-5360.

Canada
Arrow Medical Products, Ltd., 150 Britannia Road East, Unit #20, Mississauga, Ontario
L4Z 1S6. Call toll-free 800 387-7819 or in Toronto 416 890-0173.

Europe
Arrow International, Inc. (Europe), P.O. Box 345, Pampuslaan 1, 1380 A H Weesp,
The Netherlands. Phone: (0)2940-80258, Fax: (0)2159-48471.
Arrow Deutschland, G.m.b.H., Otto Hahn-Strasse 4, 8058 Erding, West Germany.
Phone: (0)8122-3026, Fax: (0)8122-40384.

Japan
Arrow Japan, Ltd., 9F Chiyoda Asahi Building, 2-8-3 Iidabashi, Chiyodaku, Tokyo 102.
Phone: 03-222-5496, Fax: 03-222-5396.
Arrow Japan, Ltd., Shin-Osaka Kita Bldg. 4F, 1–46 Miyahara 4-chome, Yodogawa-ku,

---

[1,3] Patent pending.
[2] U.S. Patent Number 4,327,723. Canadian Patent Number 4,515,[illegible].
*Refer to product labeling for information about pacing electrodes compatible with Arrow® Thermo-Pace™ Hands-Off™ catheters, or contact Arrow International, Inc.
Refer to package insert for current warnings, precautions, and instructions for use.

TRACRIUM®

Easy reversal, complete recovery

Rapid elimination of Tracrium means easy reversal and fast, complete recovery. Of all the agents in its class,* Tracrium has the shortest elimination half-life (approx. 20 min.).[1]

Low risk of residual blockade

In short and long procedures and in a wide range of patient types, its unique metabolism — unaffected by renal or hepatic dysfunction — gives Tracrium the most consistent pharmacodynamic profile of any nondepolarizing neuromuscular blocker.[2]

Outstanding record of cardiovascular safety

Documented by two recent surveillance studies: "The absence of a significant difference in cardiovascular events between the atracurium and comparison groups in the U.S. study was corroborated in the U.K. study; however in the latter, the vecuronium group experienced more cardiovascular events than the atracurium group."[3]

*Nondepolarizing neuromuscular blocking agents.

TRACRIUM® INJECTION
(atracurium besylate)

References and brief summary of full prescribing information can be found on the following page.

TRACRIUM® INJECTION

(atracurium besylate)

Ready-to-use convenience, stable 14 days on carts and trays

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: **General:** Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: **Observed in Controlled Clinical Studies:** Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* Inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

---

1. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. *Anesthesiology.* 1984;61:444-453.
2. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172.
3. Lawson DH, Paice GM, Glavin RJ, et al. Atracurium — a post-marketing surveillance study: U.K. study and discussion. *Br J Anaesth.* 1989;62:596-600.

Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Georgetown University Medical Center
and
Hopital Saint-Vincent de Paul
announce the

INTERNATIONAL SYMPOSIUM ON THE MANAGEMENT OF ACUTE AND CANCER PAIN

...Examining the Newest Developments in Pathophysiology, Pharmacology and the Treatment of Acute and Cancer Pain.

Memorial Day Weekend Paris, France

May 27-28, 1991

Spend an instructive Memorial Day Weekend in Paris with distinguished speakers from the United States and Europe, including...

J.C. Devoghel, *Belgium*
G. Guilbaud, *France*
G.W. Hanks, *Great Britain*
K. Lehmann, *Germany*
M. Pernak, *Holland*
P. Scherpereel, *France*
E. Sumner, *Great Britain*
V. Ventaffrida, *Italy*

S. Abram, *Milwaukee*
B. Bloor, *Los Angeles*
S. Naulty, *Washington*
R. Payne, *Cincinnati*
P. Raj, *Houston*
B. Ready, *Seattle*
D. Tyler, *Seattle*
P. White, *St. Louis*

Stay in luxurious hotel accomodations for a reasonabl price (approximately $1000 for travel and 4-night minimum stay) - and take optional excursions to Loir Chateaux, Mont Saint-Michel, Normandy, or other popular destinations throughout France.

Poster Presentations Available

For further information on the Scientific Program, contact:

Michel Dubois, MD
Department of Anesthesia
Georgetown University
3800 Reservoir Rd, NW
Washington, DC 20007

Phone: 202-784-3348
FAX: 202-687-8854

For further informatio on Meeting Registratio and Travel Arrangement contac

FORTRA
c/o Charles Bressl
4601 North Park Aven
Chevy Chase, MD 2081

Phone: 301-654-91
FAX: 301-652-87

The Netherlands JOURNAL OF MEDICINE

A CURRENT AND RELIABLE SOURCE OF INFORMATION FOR THE INTERNAL MEDICINE SPECIALIST

PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

Editor-in-Chief:
P.W. DE LEEUW, *Zuiderziekenhuis, Rotterdam, The Netherlands*
Associate Editors:
A.E. MEINDERS, *Leiden, The Netherlands* **A.J.M. VOGTEN,** *Heemstede, The Netherlands*

Aims and Scope:

The Netherlands Journal of Medicine publishes original articles and reviews in all relevant fields of internal medicine. In addition to clinically oriented papers, manuscripts containing experimental data, including both laboratory and animal studies, are considered for publication. The **"Br Reports"** section allows for the publication of concise reports on original work, while **Case Reports**, which are relevant for understanding the pathophysiology or clinical presentation of internal diseases may also be accepted under this heading. Furthermore, book reviews and a correspondence section are regular items in the Journal.

An International Advisory Board has been established, consisting of outstanding scientists, all distinguished investigators in various fields of inter medicine.

Since 1987 the Journal has been published in two editions: a monthly edition for the Netherlands audience and a bimonthly edition for the international audience.

Editorial Board

T.E.W. Feltkamp, *Amsterdam*
C.L.A. van Herwaarden, *Nijmegen*
R.S.G. Holdrinet, *Nijmegen*
L. Kater, *Utrecht*
A.L.M. Kerremans, *Helmond*
E.A.R. Knot, *Rotterdam*
R. Krediet, *Amsterdam-Zo*
J.F.F. Lekkerkerker, *Enschede*
J.H.M. Lockefeer, *Oisterwijk*
A.C. Nieuwenhuijzen Kruseman, *Maastricht*
L.B.A. van de Putte, *Nijmegen*
P.J.G.M. Rietra, *Amsterdam*
W.J. Remme, *Rotterdam.*
B. Sangster, *Bilthoven*
A.J.P.M. Smout, *Utrecht*
G. Stoter, *Rotterdam*
J. Thompson, *Leiden*

International Advisory Board

A. Amery, *Leuven, Belgium*
G.M. Besser, *London, U.K.*
C.J. Bulpitt, *London, U.K.*
D.L. Clement, *Gent, Belgium*
R.D. Cohen, *London, U.K.*
A.J. Czaja, *Rochester, MN, U.S.A.*
R.H. Dowling, *London, U.K.*
S. Hadziyannis, *Athens, Greece*
N. Lameire, *Gent, Belgium*
N. McIntyre, *London, U.K.*
T. Omae, *Osaka, Japan*
M. Uribe, *Mexico D.F., Mexico*
R. Vandongen, *Perth, Australia*
P.M. Vanhoutte, *Houston, TX, U.S.A.*
M.H. Weinberger, *Indianapolis, IN, U.S.A*

Cited/abstracted in: Current Contents (Clinical Medicine); Index Medicus (MEDLINE); Excerpta Medica (EMBASE) BIOSIS Database

Subscription information (Intl.Ed.):

1991: Vols. 38-39 (2 vols. in 12 issues)
Institutional rate: Dfl. 760.00/US$ 380.00
A Personal rate is available. Apply to the Publish for details.
Prices include postage and handling costs.
ISSN 0300-2977

ELSEVIER SCIENCE PUBLISHERS

For further information and/or FREE SAMPLE COPY, write to:

In the USA or Canada:
ELSEVIER SCIENCE PUBLISHING CO. INC.,
P.O. Box 882, Madison Square Station,
New York, NY 10159, U.S.A Tel: (212) 633-3750

In all other countries:
ELSEVIER SCIENCE PUBLISHERS
P.O. Box 211, 1000 AE Amsterdam,
The Netherlands.

Please send your orders to the Amsterdam address
The Dutch Guilder (Dfl.) price is definitive. US$ prices are subject to exchange rate fluctuations. Prices are excl. BTW for Dutch residents.

IARS MEMBERSHIP

FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a nonprofit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end, the IARS

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March

Funds projects in anesthesia-related research, clinical care, education, and administration through the B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, or national anesthesia organization. Membership is open to individuals who qualify in the various categories shown below. All memberships include a monthly subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee. Only IARS members may apply for the B.B. Sankey Anesthesia Advancement Award.

MEMBERSHIP CATEGORIES

MEMBERSHIP: Open to individuals with doctorate degrees who are licensed to practice in the medical, osteopathic, dental, or veterinary medicine fields (i.e., MD, MB, DO, DDS, DVM); and to individuals with doctorate degrees (PhD) in any scientific discipline who are engaged in academic, private, or commercial research.

ASSOCIATE MEMBERSHIP: Open to individuals in the allied health professions who are certified by their professional accrediting organization as nurse anesthetists (CRNA), respiratory therapists or technicians (RRT or CRTT), physician assistants (PA, MMS), and other allied health professionals in anesthesia-related practice.

Annual (1991 Calendar Year) Dues for Members and Associate Members: $90 ($110 foreign).

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists, or technicians.

Annual Dues for Educational Members: One-half of the member rate. These memberships are entered in January or July for 2-, 3-, or 4-year periods. Official application, certified by program directors, must be used and submitted with check to cover full membership period.

International Anesthesia Research Society
Suite 140-2 Summit Park Drive, Cleveland, Ohio 44131-2553

Please send me______application(s) for:

☐ Membership ☐ Associate Membership ☐ Educational Membership

Please print clearly:______________________________________

Name and Degree / Certification

____

Street Address

City, State, Zip Code (country)

CO-INDUCTION OF ANESTHESIA

A synergy of effects and advantages

Co-induction—when two or more agents rather than one are used for induction—may offer clinical benefits if there is anesthetic synergy. Specifically, subanesthetic doses of each agent may produce a prompt, short-acting effect with more stable hemodynamics than one agent alone.[1]

A classic example of synergy is mutual enhancement of receptor-site affinity: *e.g.*, a benzodiazepine such as VERSED may alter barbiturate receptors in a way that enhances barbiturate effects. Likewise, a barbiturate may potentiate a benzodiazepine by acting at its receptor sites.[2,3]

Lower doses of both agents

Several studies have shown that a small initial dose of VERSED will allow lower induction doses of thiopental, methohexital, fentanyl, alfentanil or ketamine.[1,4-9]

In one study of 90 unpremedicated ASA Class I & II patients, co-induction with VERSED followed by thiopental required just 1/4 of each drug's usual ED_{50}.[5]

Lower risk of breakthrough awareness

VERSED produces a marked amnestic effect. Therefore, a VERSED co-induction may reduce the possibility of recall (*e.g.*, during intubation) in the event of lightening of anesthesia with short-acting hypnotics such as thiopental or propofol.

Dosing considerations with VERSED® (midazolam HCl/Roche)Ⓒ

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.*, drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

IDEAS IN ANESTHESIA

AN ONGOING SERIES

Roche Laboratories
a division of Hoffmann-La Roche Inc.

Copyright © 1991 by Hoffmann-La Roche Inc. All rights reserved.

Please see summary of product information on following page.

References: 1. Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. 2. Skolnick P, *et al.* Pentobarbital: dual actions to increase brain benzodiazepine receptor affinity. *Science.* March 1981;211:1448-1450. 3. Miller LG, *et al.* Acute barbiturate administration increases benzodiazepine receptor binding in vivo. *Psychopharmacology (Berlin).* 1988;96:385-390. 4. White FF. Comparative evaluation of intravenous agents for rapid sequence induction—thiopental, ketamine and midazolam. *Anesthesiology.* 1982;57:279-284. 5. Tverskoy M, *et al.* Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. 6. Tverskoy M, *et al.* Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth.* 1989;63:109-112. 7. Kissin I, *et al.* Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesth Analg.* 1990;71:65-69. 8. Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. 9. Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47.

VERSED®
(brand of midazolam HCl/Roche)Ⓒ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

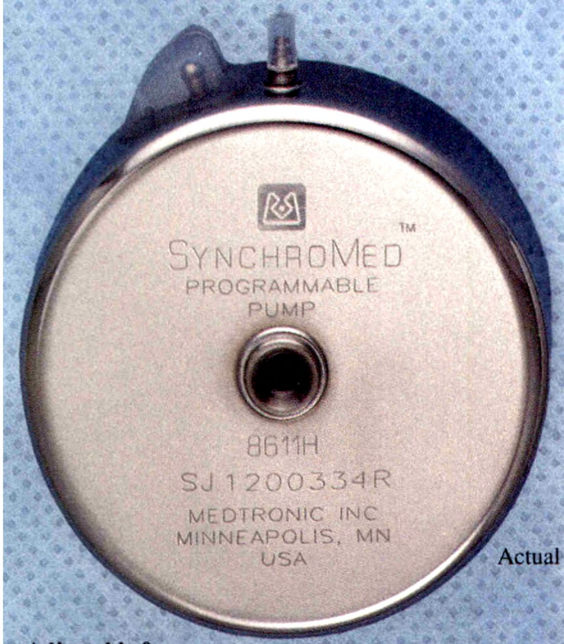
DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

PJ. 0968

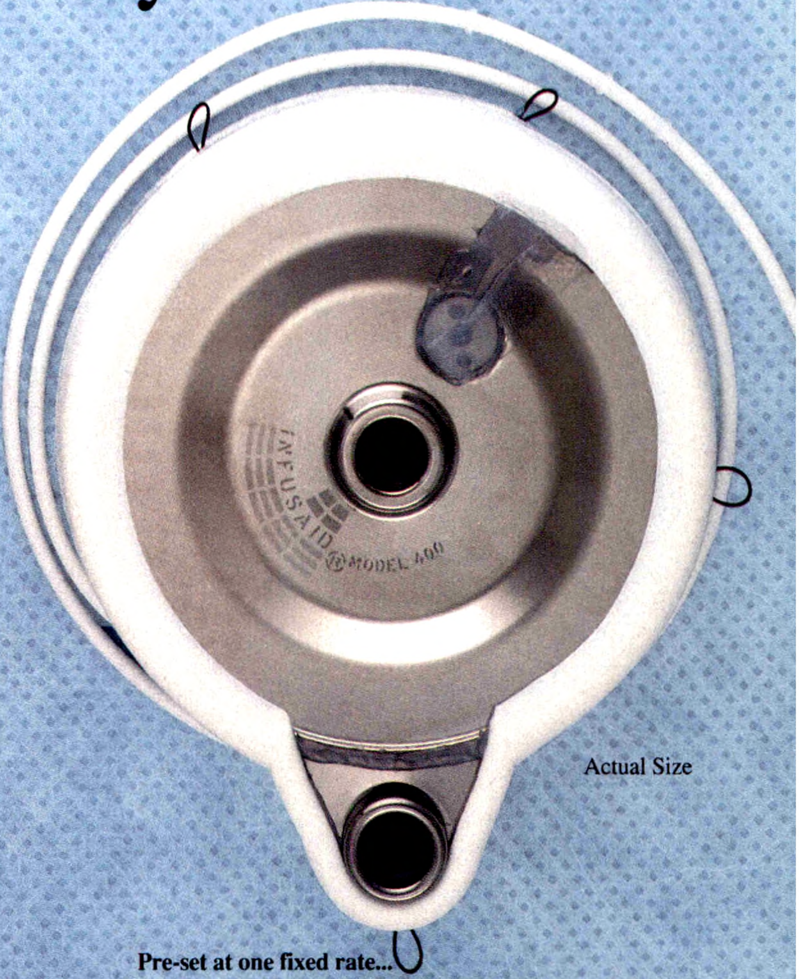
Roche Laboratories
a division of Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

Only one implantable is smart enough to follow all of your orders.

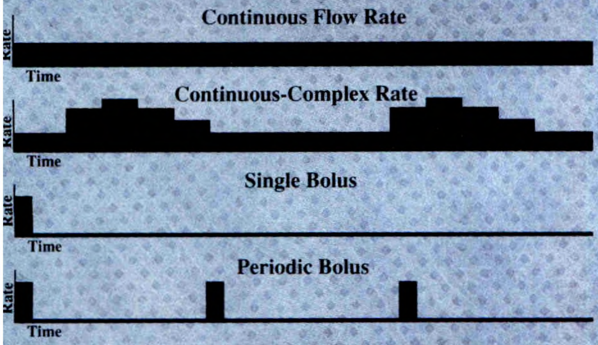


Actual Size

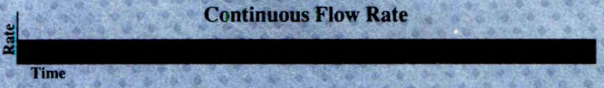


Actual Size

Adjustable from 0.1 to 18 ml/day...



Pre-set at one fixed rate...



SynchroMed® Programmable Pump does exactly what you want it to do.

Non-programmable alternative does only what it was built to do.

With the SynchroMed Programmable Pump, **flow rate is easily programmed** for whatever variable or continuous infusion schedule you think is best. Accuracy is unaffected by the environment. And, as patient requirements change, flow rate adjustment is non-invasive for comfort and safety.

More than just follow orders, the pump can tell you the patient's I.D., drug type, concentration, remaining volume, flow rate and date last programmed.

This combination of flexibility, precision and responsiveness is impossible with the non-programmable unit which operates only at the rate built in by the manufacturer.

The SynchroMed Pump is also smaller and almost 50 g lighter when filled. Yet, it **requires fewer refills.** With computer-based technology engineered into the compact device, flow rates can be lower, and refill periods longer. For refills, you can readily **use pre-mixed concentrations** and save time in the pharmacy.

If you'd like to further evaluate the benefits of the only implantable programmable pump commercially available, contact us for more information and free educational materials.

Medtronic

Medtronic Neurological Division 800 53rd Avenue N.E. Minneapolis, MN 55421 Attn: N340-DH 800-328-0810 / 612-572-5000

Copyright © 1991 by Medtronic, Inc. Minneapolis, Minnesota USA

SYNCHROMED®
INFUSION SYSTEM

The Implantable Pump with External Control

Indications

The SynchroMed Infusion System is indicated for use when patient therapy requires the chronic intravascular infusion of floxuridine or doxorubicin. In addition, the nontherapeutic use of bacteriostatic water, physiological saline, and/or heparin is indicated necessary to support this mode of cancer therapy.

The regional intra-arterial infusion of floxuridine is used in the palliative management of unresectable solid colorectal tumors metastatic to the liver.

The systemic intravenous infusion of doxuribicin is used in the palliative management of various solid tumors, lymphomas, and leukemias.

Bacteriostatic water or physiological saline can be used to achieve the physician-prescribed concentration of floxuridine or doxorubicin or to flush the pump reservoir. Heparinized physiological saline may be used during an interruption in floxuridine therapy to maintain catheter patency.

Physicians prescribing the SynchroMed Infusion System for use with floxuridine or doxorubicin sterile solution must be familiar with the indications, contraindications, and warnings described in the drug labeling. Except under approved conditions of Investigational Device Exemptions, the use of the SynchroMed Infusion System is restricted to the infusion of the drugs and fluids previously described.

Contraindications

The device should not be implanted in the presence of infection.

mplantation is contraindicated when the pump cannot be implanted less than 2.5 cm (one inch) from the surface of the skin and/or when the patient has an implanted programmable medical device.

Patients whose body size is not sufficient to accept the pump bulk and weight are not suitable.

Contraindications relating to the use of the prescribed drug should be observed.

Copyright 1991 Medtronic, Inc.
NP-1304 UC9003081EN

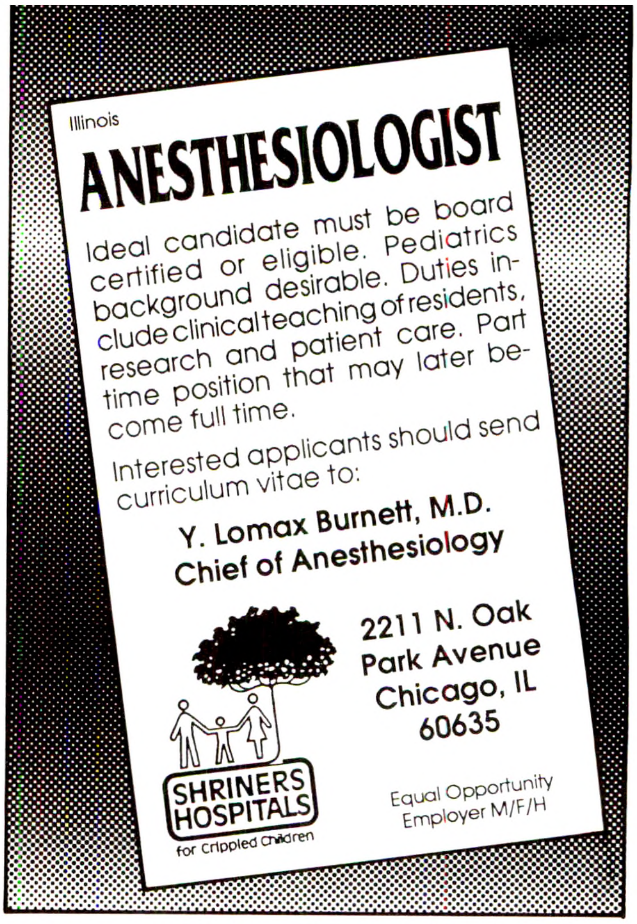
All rights reserved.

Jnited States of America
ledtronic Neurological
00 53rd Avenue, N.E.
linneapolis, MN 55421
elephone: (612) 572-5000
AX: (612) 572-5078
oll-Free: 1-800-328-0810

anada, Latin America
ledtronic of Canada, Ltd.
733 Kitimat Road
lississauga, Ontario L5N 1W3
anada
elephone: (416) 826-6020
AX: (416) 826-6620
oll-free: 1-800-268-5346

Europe
Medtronic Europe
25 rue Chateaubriand
75008 Paris, France
Telephone: (33-1) 42-56-46-88
Telex: 643-449
FAX: (33-1) 42-56-07-66

Asia-Pacific
Medtronic Asia-Pacific
Shuwa Kioi-cho Park
Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (03) 230-2919
Telex: J23920 HYMEDTRO
FAX: (03) 230-0446



Illinois

ANESTHESIOLOGIST

Ideal candidate must be board certified or eligible. Pediatrics background desirable. Duties include clinical teaching of residents, research and patient care. Part time position that may later become full time.

Interested applicants should send curriculum vitae to:

Y. Lomax Burnett, M.D.
Chief of Anesthesiology

2211 N. Oak
Park Avenue
Chicago, IL
60635

SHRINERS HOSPITALS
for Crippled Children

Equal Opportunity Employer M/F/H

CLEVELAND CLINIC

The Department of Cardiothoracic Anesthesia, Cleveland Clinic Foundation is seeking applications from those interested in 6 months or one-year CA 3/4 subspecialty training. The experience encompasses the perioperative management of over 4000 patients scheduled for all major cardiac and thoracic procedures. Such positions are available in July, 1991 or January, 1992. Opportunities for clinical research accompany the vast clinical training.

Interested candidates should write to:

Dr. Erik J. Kraenzler
Department of Cardiothoracic Anesthesia
G-3
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44195

THERE'S J ST ONE THING MISSING AT ANESTHESIA PARTNERS...

U

And we may *just* have the opportunity you've been looking for! Practice your specialty as part of a team of physicians and CRNAs backed by our professional and reliable recruitment, staffing, billing and credentialing services. You can enjoy an outstanding liability insurance program, access to an excellent benefits package and competitive remuneration programs.

Anesthesia Partners, Inc. was established to provide anesthesiology staffing and management services nationwide to healthcare facilities on an extended contractual basis. You can enjoy the financial rewards associated with fee-for-service arrangements without the concerns of collecting patient accounts and carrying receivables.

There's just one thing missing at Anesthesia Partners...It's you!

ANESTHESIA
PARTNERS, INC.

Partners in Health Care Management™

If you are interested in opportunities with Anesthesia Partners, Inc., contact Medical Staff Development at 1-800-476-9551.

Say Yes To Michigan!

ANESTHESIOLOGISTS

BE/BC Anesthesiologist to join a six (6) member group and CRNS'S. Group performs over 12,000 cases per year ie. open heart, minimum obstetrics and pediatrics mostly general surgery. Full partnership after one year. Excellent call coverage. Highly competitive compensation. Affiliated with a large teaching hospital in mid-eastern Michigan. The Great Lakes and the recreational opportunities of the four seasons make Michigan a wonderful place to live and work. Please contact our staff in confidence at:

Physician Practice Link
1120 Eisenhower Pl., Bldg #1
Ann Arbor, MI 48104-7448

In Michigan 1-800-431-LINK
In U.S. 1-800-322-LINK
Fax: (313) 677-0142

STAFF ANESTHESIOLOGISTS

St. Luke's/Roosevelt Hospital Center, affiliated with the Columbia University College of Physicians and Surgeons, and one of New York City's largest voluntary hospitals, has several faculty positions available at Assistant and Associate Professor level.

Prerequisites are a 3 year residency, board certification or eligibility, New York State license or eligibility, and eligibility for faculty appointment at Columbia University. Special qualifications in pain, critical care, neuro, obstetric, and cardiac anesthesia are highly desirable. Interest in teaching and research are essential.

Competitive remuneration and fringe benefits. Send curriculum vitae to **Daniel M. Thys, M.D., Director, Department of Anesthesiology, St. Luke's/Roosevelt Hospital Center, Amsterdam Avenue at 114th Street, New York, N.Y. 10025**. St. Luke's/Roosevelt Hospital Center takes affirmative action to ensure equal opportunity.

ST. LUKE'S\ROOSEVELT
Hospital Center

ANESTHESIOLOGY RESEARCH FELLOWSHIPS IN ANESTHETIC PHARMACOLOGY

The Department of Anesthesiology at Vanderbilt University is looking for Board eligible anesthesiologists for both basic and clinical research training in preparation for a career in academic medicine. The training program consists of full time laboratory and clinical investigation with no "on call" duties for a one, or preferably two, year period. Examples of areas of investigation include: Cardiovascular anesthetic physiology and pharmacology, drug metabolism and anesthesia, pharmacokinetics and anesthesia, and pharmacogenetics and anesthesia. The fellowships are supported by the NIH.

Address enquiries to:

Margaret Wood, M.D.
Professor of Anesthesiology
Department of Anesthesiology
Vanderbilt University
Medical School
Nashville, TN 37232-2125

Vanderbilt
University
School of Medicine

Nurse Anesthetist

The University Hospital and Clinics, a 440-bed level I Trauma Center, has a position with our busy Surgery Services Department. As a regional teaching, research and referral hospital, we administer anesthetics for all specialties. We also have a challenging physician residency program.

Located in the heart of Missouri, Columbia offers a unique blend of cultural, educational and recreational opportunites. Our outstanding living environment features a low cost of living, nationally recognized public schools and a variety of housing options.

Find out about joining us on the Staff for Life! Interested applicants should submit a resume to: **Nurse Recruitment; University Hospital and Clinics; One Hospital Drive; Columbia, MO 65212, or call (314) 882-8701 or 1-800-622-6914.**

University
Hospital & Clinics
The Staff for Life

An Affirmative Action/Equal Opportunity Employer

IARS

NEW OFFICE ADDRESS

Effective October 1, 1990, the **International Anesthesia Research Society** headquarters office in Cleveland moved to the following new address:

International Anesthesia
Research Society
Suite 140, 2 Summit Park Drive
Cleveland, Ohio 44131-2553

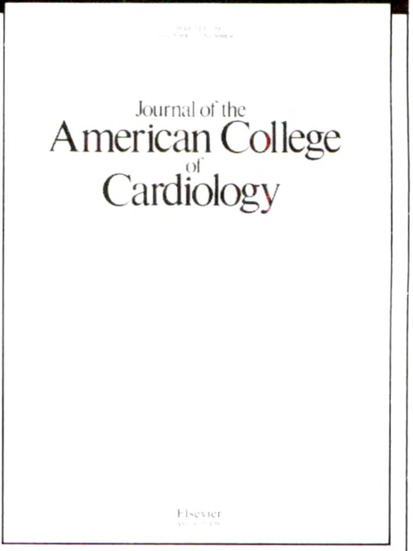
NEW TELEPHONE NUMBER:
(216) 642-1124

All membership payments and correspondence regarding **IARS** member subscriptions, annual scientific meeting matters, the B.B. Sankey Anesthesia Advancement Award, etc., should be sent to the above address.

Follow the Leader in Cardiology

Read JACC monthly

Journal of the American College of Cardiology



Journal of the
American College
of
Cardiology

Elsevier

The Journal of the American College of Cardiology, **JACC**, is the leading journal in cardiology. **JACC's** timely coverage of clinically relevant information on the diagnosis and treatment of cardiovascular diseases has made it a favorite among cardiologists worldwide.

Why not join the thousands of your colleagues who have made reading **JACC** a part of their regular routine?

Read the **Journal of the American College of Cardiology** each month and you will find a superb collection of original articles, clinical reviews, special reports, and editorials at the forefront of cardiovascular medicine. **JACC's** comprehensive focus and distinguished editorial board assure you the most significant new information—information that you can apply directly to your practice.

Discover why **JACC** is the #1 journal in cardiology. Enter your subscription today and follow the most current and authoritative source on important developments in cardiology.

Journal of the American College of Cardiology
Volumes 17, 18 (14 issues + 1 supplement)
ISSN 0735-1097

Personal Rate: $88.00*
Institutional Rate: $132.00
Intern/Resident Rate: $55.00†

Subscribers in the U.S., Canada, or Mexico may request air delivery for an additional $115.00. Subscribers outside the U.S. must add one of the following postage options: $60.00 (surface delivery); $160.00 (surface air lift/Europe); $210.00 (surface air lift/Japan); or $305.00 (air/rest of world).

Note: All subscriptions begin with the first issue of the calendar year and are entered upon receipt of payment. Please allow 4-6 weeks for delivery of your first journal issue. Subscription rates valid until December 31, 1991.

* The personal rate is available to individuals only. A home, hospital or medical school address must be used for delivery. Orders from non-U.S. customers must be prepaid.

† Intern/Resident Rate is valid for two years only. Please send proof of status.

For sample copies send to:
in North America: Elsevier
Science Publishing Co., Inc.,
P.O. Box 882,
Madison Square Station
New York, New York 10159
in the rest of the world:
Elsevier Science Publishers,
Direct Mail Department
P.O. Box 211, 1000 AE
Amsterdam,The Netherlands

ELSEVIER
SCIENCE PUBLISHING
COMPANY, INC.

Send subscription orders to your usual supplier or the New York address. For even faster service, call
(212) 633-3950 or fax
(212) 633-3880

X7AQ
9/90

BIAE048A

ANNUAL MIDWEST Pediatric ANESTHESIA MEETING

Illinois Masonic Medical Center Presents
Annual Midwest Pediatric Anesthesia Meeting & Annual Chicago Obstetrical Anesthesia Meeting

April 11–14, 1991 Holiday Inn Mart Plaza

ANNUAL CHICAGO Obstetrical ANESTHESIA MEETING

FACULTY — DOCTORS

Birmingham, Burnett, Cook, Czinn, Dsida, Gregory, Hall, Horn, Hyman, Klowden, Krishna, Lerman, Manley, Mazurek, Przybylo, Salem, Stevenson, Uejima, Welborn.

Albright, Curran, Finster, Gibbs, Heyman, Joyce, Kassa, Nimmagadda, Ostheimer.

Pediatric Anesthesia Topics

- Resuscitation of the Newborn
- The Economics and Politics of Health Care Delivery
- Transitional Tasks of the Newborn
- Respiratory and Cardiovascular Physiology in the Neonate
- New Inhalation Anesthetics
- Narcotics in Neonatal Anesthesia
- Pharmacology of Inhalational Anesthetics in Infants and Children
- Anesthesia for Premature Infants
- New Short Acting Muscle Relaxants
- Succinylcholine—Friend or Foe?
- Oral Premedication
- The Fasting Dilemma
- Post Operative Apnea in the Former Preterm Infant
- Neonatal Emergencies
- Neonatal Pain Therapy
- Pathophysiological Principles of Congenital Heart Disease
- Anesthesia for the Treatment of Congenital Heart Diesease
- Anesthesia for the Cardiac Patient Undergoing Non-Cardiac Surgery
- Coagulation Problems in the Pediatric Patient
- Blood Conservation Measures in Pediatric Patients—Part I
- Blood Conservation Measures in Pediatric Patients—Part II
- Perioperative Blood Glucose Changes in Pediatric Patients
- Glucose: Who Needs It?
- Malignant Hyperthermia—Old Disease New Problems
- Parental Participation in Anesthetic Induction—Necessary or Nice?
- One Lung Anesthesia
- ECMO—Who Needs It?
- Propofol in Pediatric Anesthesia
- Anesthesia and the Anemic Child
- Anesthesia for Endoscopic Procedures
- Anesthesia for Pediatric Neurosurgery
- Anesthesia Outside the Operating Room
- Anesthesia for Scoliosis Correction
- Anesthesia for Muscular Dystrophies
- Anesthesia for the Infant with a Myelomeningocele
- Special Pediatric Problems in the Post Anesthesia Recovery Area
- Anesthesia for Pyloromyotomy
- Anesthesia for Pediatric Trauma
- Considerations for Pediatric Equipment
- The Child with Sickle Cell Disease

Obstetrical Anesthesia Topics:

- Resuscitation of the Newborn
- The Economics and Politics of Health Care Delivery
- Physiology of Pregnancy
- Anesthesia and Uterine Blood Flow
- Obstetric Medication and Anesthetic Interaction
- Do We Make Too Much of a Fuss About Pulmonary Aspiration?
- Is There a Place for General Anesthesia in Obstetrics?
- Epidural Anesthesia for Cesarean Section
- Effects of Epidural Blocks on Labor and Delivery
- New Drugs in Obstetrical Anesthesia: Propofol and Organon 9426
- History of Obstetric Anesthesia
- Drug Exposure of the Preterm Fetus
- Continuous Infusion Epidurals—What Drugs?
- The Use of Epidural and Subarachnoid Opiates in Obstetrics
- The Future of Standards in Obstetrical Anesthesia
- Neological Injuries in the Obstetrical Patient That Are Not Our Fault
- Does Pregnancy Enhance Local Anesthetic Toxicity?
- Spinal Headaches—Prevention and Management
- Pitfalls in Obstetric Anesthesia Practice in the Community Hospital
- Anesthesia Considerations in Obstetrical Hemorrhage
- Hemodynamic Alterations in Pre-Eclampsia/Eclampsia
- Anesthesia for the Parturient with Heart Disease
- Anesthesia for the Pregnant Surgical Patient
- Anesthesia for In-Vitro Fertilization

For Information Contact: Department of Anesthesiology, Illinois Masonic Medical Center, 836 W. Wellington, Chicago, Illinois Telephone: 312/883-7035/7041. The courses are approved for 25 hours each. Category I

The Department of Anesthesiology, University of Texas Health Science Center at San Antonio

Announces an important workshop prior to the 65th Congress of the International Anesthesia Research Society

APPLICATIONS OF TRANSCRANIAL DOPPLER (TCD) MONITORING IN ANESTHESIOLOGY

Friday, March 8, 1991 — Marriott Rivercenter Hotel — San Antonio, Texas

7:30 - 8:30 a.m.	Registration and Continental Breakfast
8:30 - 12:00 p.m.	Presentations on TCD Monitoring
12:30 - 2:00 p.m.	Luncheon
1:00 - 5:30 p.m.	Workshops on TCD Monitoring

Chairman—Maurice S. Albin, M.D., M.Sc. (Anes.)

Introduction to TCD - Physics and Intracranial Anatomy
Merrill Spencer, M.D.

TCD Monitoring in Carotid Endarterectomy
James Halsey, M.D.

TCD Monitoring in Infants and Children
Brono Bissonnette, M.D.

TCD Monitoring in Pediatric Cardiopulmonary Bypass
Paul Hickey, M.D.

TCD Monitoring in Adult Cardiopulmonary Bypass
Maurice S. Albin, M.D., M.Sc. (Anes.)

TCD Monitoring in Head Trauma
Arthur Lam, M.D.

TCD Monitoring Related to Other Modalities
William Young, M.D.

Eight (8) hours of CME credit will be granted for attendees. The subscription cost is $175.

For further information, please contact:
Continuing Medical Education
University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, Texas 78284-7980
Phone # (512) 567-4444

Are patients' drugs of choice... going to affect your drugs of choice?

Anesthetics can interact with many illegal drugs, causing arrhythmias and other complications.[1]

Always ask about drug abuse in your presurgical interview.

And be prepared for possible complications of drug abuse in trauma patients.

Or your patients may have no choices left.

1. Rowbotham MC: Neurologic aspects of cocaine abuse (Medical Staff Conference). *West J Med* 1988;149:442-448.

Partnership for a Drug-Free America

ANESTH ANALG 1991;72:169–76

Leukotriene Synthesis Inhibition and Receptor Blockade Do Not Inhibit Hypoxic Pulmonary Vasoconstriction in Sheep

Ronald G. Pearl, MD, PhD, and Richard C. Prielipp, MD

PEARL RG, PRIELIPP RC. Leukotriene synthesis inhibition and receptor blockade do not inhibit hypoxic pulmonary vasoconstriction in sheep. Anesth Analg 1991; 72:169–76.

Several lines of evidence suggest that leukotrienes may be mediators of hypoxic pulmonary vasoconstriction (HPV). However, the effect of leukotriene inhibition on HPV remains controversial. The present study investigated the effect of leukotriene synthesis inhibition and receptor blockade on HPV in the halothane-anesthetized sheep. After initial baseline measurements, the pulmonary pressor response to 15 min of global hypoxia (F_{IO_2} = 0.13) was measured. A second set of baseline measurements was obtained and the sheep then received the combined cyclooxygenase/lipoxygenase inhibitor BW755C, the selective lipoxygenase inhibitor U60257, or the leukotriene receptor antagonist LY171883. Hemodynamic measurements were obtained after drug administration and during a subsequent hypoxic challenge (F_{IO_2} = 0.13). Initial hypoxic challenge increased pulmonary artery pressure 68% and increased pulmonary vascular resistance 104%. Pulmonary hemodynamics after recovery from hypoxia were similar to initial baseline values. Drug administration had no significant hemodynamic effect. Hypoxic challenge after drug administration resulted in a pulmonary pressor response identical to the initial hypoxic challenge. Because leukotriene synthesis inhibition and receptor blockade did not alter the response to hypoxia, we conclude that leukotrienes are not obligatory mediators of HPV. A critical review of the literature supports a modulatory rather than an obligatory role for leukotrienes in HPV.

Key Words: HORMONES, PROSTAGLANDINS—leukotrienes. LUNG, HYPOXIC PULMONARY VASOCONSTRICTION—vascular resistance. LUNG, METABOLISM—arachidonic acid, cyclooxygenase, lipoxygenase.

Hypoxic pulmonary vasoconstriction (HPV) was originally described in the cat as a global pulmonary pressor response to hypoxia (1). Since this original description by von Euler and Liljestrand in 1946, HPV has been extensively investigated in many species (2,3). The mediators of HPV, however, remain unknown. One possible group of mediators are the peptidoleukotrienes. Exogenous leukotriene administration produces pulmonary vasoconstriction in multiple species (4–7). Leukotrienes are synthesized in the lungs and released during hypoxic exposure (8–10). Inhibition of leukotriene synthesis, leukotriene release, or leukotriene receptors can inhibit HPV in both in vivo and in vitro models (9–20). However, failure to inhibit HPV with similar or identical agents in other studies has raised questions about the role of leukotrienes as mediators of HPV (5,18,21–31). The current study was therefore designed to investigate the effects of leukotriene synthesis inhibition (using the combined cyclooxygenase/lipoxygenase inhibitor BW755C or the selective lipoxygenase inhibitor U60257) and of leukotriene receptor blockade (using LY171883) on the effects of HPV in the anesthetized sheep.

Methods

The protocol for this study was approved by the Stanford Panel on Laboratory Animal Care.

After an overnight fast, 21 male sheep weighing 17–30 kg were anesthetized with 20 mg/kg intravenous thiopental. Sheep were intubated with a cuffed endotracheal tube and mechanically ventilated at a tidal volume of 15 mL/kg and at a rate adjusted to maintain arterial carbon dioxide tension (Pa_{CO_2}) between 35 and 45 mm Hg. Anesthesia was maintained

---

Supported in part by a grant from the American Lung Association of California Research Program of the American Lung Association of California.

Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California, and the Department of Anesthesiology, Bowman Gray School of Medicine, Winston Salem, North Carolina. Accepted for publication October 3, 1990.

Address correspondence to Dr. Pearl, Department of Anesthesia, Stanford University Medical Center, Stanford, CA 94305-5117.

©1991 by the International Anesthesia Research Society

with halothane (1% end-tidal concentration) throughout the study. After induction of anesthesia, systemic arterial, central venous, and triple-lumen pulmonary artery catheters were inserted by peripheral cutdown. One hour later, initial baseline measurements (baseline 1) during ventilation with halothane in oxygen ($F\text{IO}_2$ = 0.99) were obtained. Measured variables included heart rate, mean systemic arterial pressure ($\bar{P}$sa), mean pulmonary arterial pressure ($\bar{P}$pa), pulmonary artery occlusion pressure ($\bar{P}$pao), cardiac output ($\dot{Q}_t$), and arterial blood gas tensions (Pao_2, Paco_2) and pH.

After baseline measurements, inspired oxygen concentration ($F\text{IO}_2$) was reduced to 0.13 using a calibrated gas mixture of oxygen and nitrogen with 1% halothane; $F\text{IO}_2$ was confirmed by direct measurement of inspired gas Po_2 (98–100 mm Hg) in each animal. Measurements were obtained after 15 min of hypoxia (hypoxia 1). Sheep were then ventilated with 1% halothane in oxygen, and a second set of baseline measurements (baseline 2) was obtained 1 h later.

A leukotriene synthesis or receptor blocker (BW755C, n = 8; LY171883, n = 7; U60257, n = 6) was then administered and measurements were obtained 5 min after drug administration. The inspired oxygen concentration was then reduced to 0.13, and a final set of measurements was obtained after 15 min of hypoxia (hypoxia 2).

Measurement Techniques

Intravascular pressures were measured at end-expiration with disposable pressure transducers (Trantec 2000) referenced to left atrial level and recorded on a Hewlett-Packard eight-channel stripchart recorder. Heart rate was measured by continuous electrocardiographic monitoring. Cardiac output was determined in triplicate by thermodilution technique using 10 mL of room-temperature saline injectate and an Edwards 9520A cardiac output computer. Blood gases were analyzed using a Corning 168 pH/blood gas analyzer. End-tidal halothane concentration was measured with a Puritan-Bennett Anesthetic Agent Monitor. Pulmonary vascular resistance was calculated as ($\bar{P}$pa − $\bar{P}$pao) × 80/$\dot{Q}$.

Drugs

BW755C, LY171883, and U60257 (piriprost) were gifts from Burroughs Wellcome, Lilly, and Upjohn, respectively, and were formulated and administered as suggested by the companies. BW755C was dissolved in saline and administered at an intravenous dose of 10 (n = 3) or 20 (n = 5) mg/kg over 1 h. LY171883 sodium was dissolved in saline (20 mg/mL) and administered at an intravenous dose of 30 mg/kg over 30 min. U60257 was dissolved in saline (20 mg/mL) and administered at a dose of 20 mg as a nebulized aerosol over 5 min.

Statistical Analysis

Data are expressed as mean ± SEM and analyzed by a two-factor (drug × time) repeated measures analysis of variance followed by the Newman–Keuls multiple range test when appropriate. $P < 0.05$ was considered to be significant.

Results

There were no significant differences in any hemodynamic or blood gas variables among the three groups at any time point (Tables 1 and 2). Initial hypoxic challenge (hypoxia 1) increased $\bar{P}$pa by 70%, 79%, and 55% in the BW755C, LY171883, and U60257 groups, respectively, and increased pulmonary vascular resistance by 109%, 113%, and 91% in the three groups, respectively (Table 1, Figure 1). Hypoxia did not alter any other hemodynamic variables. Hypoxia decreased Pao_2 but did not affect Paco_2 or pH. After recovery from hypoxia 1, baseline 2 measurements were not significantly different from baseline 1 values. Administration of each of the three drugs did not significantly alter any hemodynamic or blood gas variable. Hypoxic challenge (hypoxia 2) after drug administration increased $\bar{P}$pa by 78%, 86%, and 64% and increased pulmonary vascular resistance by 98%, 86%, and 85%, respectively, in the BW755C, LY171883, and U60257 groups. Values during hypoxia 2 were not significantly different from values during hypoxia 1.

Discussion

In the current study, administration of BW755C, LY171883, and U60257 did not alter the pulmonary pressor response to hypoxia in halothane-anesthetized male sheep. We have previously demonstrated in control sheep that the pulmonary pressor response to a second hypoxic challenge is identical to the response to the first hypoxic challenge (28). We therefore conclude that the three drugs as administered in the current study did not alter HPV. The

Table 1. Hemodynamic Effects of Drug Treatment and Hypoxia

	Baseline 1	Hypoxia 1	Baseline 2	Drug	Hypoxia 2
$\bar{P}$pa (mm Hg)					
BW755C	14.5 ± 2.2	24.7 ± 3.1^{a}	15.7 ± 2.2	16.2 ± 2.3	28.9 ± 3.4^{a,b}
LY171883	11.7 ± 1.4	20.9 ± 1.9^{a}	13.2 ± 1.3	13.2 ± 1.8	24.5 ± 3.2^{a,b}
U60257	13.9 ± 1.1	21.5 ± 1.4^{a}	14.4 ± 1.4	14.8 ± 1.8	24.3 ± 1.9^{a,b}
PVR (dyne·s·cm^{-5})					
BW755C	291 ± 50	609 ± 98^{a}	319 ± 64	262 ± 43	520 ± 68^{a,b}
LY171883	220 ± 25	468 ± 73^{a}	300 ± 48	272 ± 37	505 ± 90^{a,b}
U60257	217 ± 18	415 ± 44^{a}	217 ± 18	231 ± 50	427 ± 65^{a,b}
$\bar{P}$pao (mm Hg)					
BW755C	6.0 ± 1.0	6.6 ± 1.3	5.9 ± 1.1	6.5 ± 1.2	6.8 ± 1.5
LY171883	5.1 ± 1.2	5.2 ± 1.2	5.2 ± 1.3	5.4 ± 1.4	5.2 ± 1.5
U60257	6.5 ± 1.0	6.9 ± 1.0	6.8 ± 1.1	6.9 ± 1.3	7.5 ± 1.1
$\bar{P}$sa (mm Hg)					
BW755C	86 ± 4	82 ± 5	85 ± 5	88 ± 6	82 ± 6
LY171883	86 ± 5	89 ± 5	83 ± 8	74 ± 8	79 ± 10
U60257	100 ± 4	93 ± 8	93 ± 5	100 ± 3	101 ± 5
$\dot{Q}_t$ (L/min)					
BW755C	2.44 ± 0.25	2.66 ± 0.33	2.77 ± 0.41	3.22 ± 0.45	3.97 ± 0.73^{a}
LY171883	2.18 ± 0.07	2.65 ± 0.32	2.18 ± 0.19	2.39 ± 0.15	2.87 ± 0.38
U60257	2.75 ± 0.25	2.97 ± 0.36	2.88 ± 0.34	2.87 ± 0.29	3.42 ± 0.47
HR (beats/min)					
BW755C	125 ± 7	141 ± 30	128 ± 17	138 ± 24	167 ± 33^{a,b}
LY171883	118 ± 10	134 ± 14	124 ± 11	144 ± 8	127 ± 19
U60257	125 ± 10	146 ± 11	129 ± 10	133 ± 10	162 ± 18^{a,b}

PVR, pulmonary vascular resistance; $\bar{P}$pa, mean pulmonary artery pressure; $\bar{P}$pao, pulmonary artery occlusion pressure; $\bar{P}$sa, mean systemic arterial pressure; $\dot{Q}_t$, cardiac output; HR, heart rate.

[a] $P < 0.01$ compared with corresponding baseline value.

[b] $P < 0.01$ compared with prior drug value.

Table 2. Arterial Blood Gas Tensions and pH

	Baseline 1	Hypoxia 1	Baseline 2	Drug	Hypoxia 2
pH (U)					
BW755C	7.40 ± 0.13	7.44 ± 0.02	7.40 ± 0.02	7.40 ± 0.01	7.40 ± 0.01
LY171883	7.43 ± 0.05	7.43 ± 0.04	7.46 ± 0.05	7.44 ± 0.05	7.44 ± 0.04
U60257	7.41 ± 0.03	7.45 ± 0.04	7.42 ± 0.02	7.42 ± 0.02	7.43 ± 0.02
Pao_2 (mm Hg)					
BW755C	500 ± 14	34 ± 1^{a}	478 ± 21	491 ± 21	31 ± 2^{a,b}
LY171883	511 ± 12	44 ± 3^{a}	483 ± 30	541 ± 14	38 ± 2^{a,b}
U60257	463 ± 11	41 ± 2^{a}	479 ± 22	485 ± 29	36 ± 1^{a,b}
Paco_2 (mm Hg)					
BW755C	38 ± 1	33 ± 2	39 ± 2	38 ± 1	37 ± 2
LY171883	35 ± 2	37 ± 3	34 ± 2	35 ± 2	36 ± 1
U60257	40 ± 2	35 ± 2	37 ± 1	36 ± 2	36 ± 2

Values are expressed as mean ± SEM.

[a] $P < 0.01$ compared with corresponding baseline value.

[b] $P < 0.01$ compared with prior drug value.

failure to inhibit HPV suggests either that leukotrienes are not required for HPV in this model or that the blockers used did not alter leukotriene effects in this model, or both. Our choice of drug doses, formulation, and rate of administration was based on the manufacturers' suggestions and extrapolation from the literature; however, in the absence of measurement of leukotriene levels or of assessment of the blockade of exogenous leukotriene effects, we cannot be certain that the agents were effective. Although the use of ineffective doses may explain the failure to inhibit HPV with one or more of the agents, we consider it extremely unlikely that all three agents were ineffective in affecting leukotriene synthesis and effects. Our findings therefore suggest that leukotrienes do not mediate HPV in halothane-anesthetized

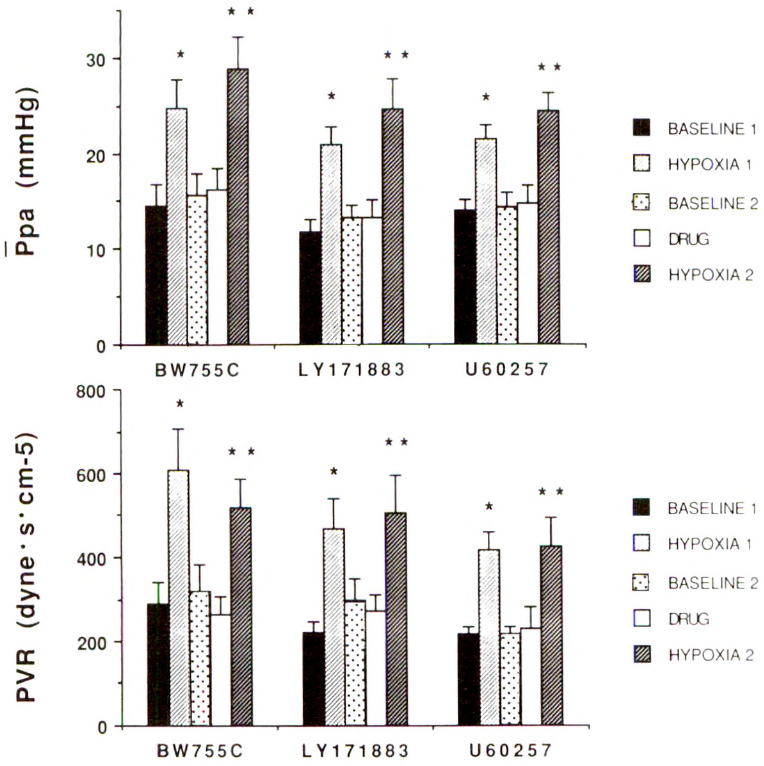


Figure 1. Mean pulmonary artery pressure (P̄pa) and pulmonary vascular resistance (PVR) during initial baseline (baseline 1), first hypoxic challenge (hypoxia 1), repeat baseline (baseline 2), after drug treatment with BW755C, LY171883, or U60257, and during second hypoxic challenge (hypoxia 2). *$P < 0.01$ versus baseline 1. **$P < 0.01$ versus baseline 2 and versus drug.

sheep, a conclusion consistent with our report that cromolyn sodium, which inhibits leukotriene release from mast cells, does not alter HPV in this model (28).

Other investigators have demonstrated a potential role for the peptidoleukotrienes as mediators of HPV. Leukotrienes are synthesized in the lung (8) and released during hypoxic exposure (9). Exogenous administration of leukotrienes causes pulmonary vasoconstriction in sheep (6,7), pigs (5), and cats (4). Inhibition of leukotriene synthesis, leukotriene receptors, or leukotriene release may inhibit HPV in perfused lung, anesthetized animal, and conscious animal models (9–20) (Table 3). The above evidence implicates leukotrienes as potential mediators of HPV. However, other studies using similar models have not been able to inhibit HPV with leukotriene synthesis inhibitors, receptor antagonists, or mast-cell stabilizers (5,18,21–31) (Table 3). The present study adds to this growing body of evidence that leukotrienes are not obligatory for HPV.

Table 3 summarizes many of the studies of the effects of leukotriene inhibition of HPV. The studies differ in the choice of drugs, species (sheep, dog, pig, ferret, rat) sex, age (newborn versus adult), model (perfused lung versus intact animal), the use of anesthesia, and the timing of hypoxia. Although each of these variables may affect the hypoxic pulmonary response (32–36), Table 3 indicates that none of the variables appears sufficient to explain the conflicting results. The results of the current study are best understood by a detailed review of the effects on HPV of the major categories of drugs studied.

Arachidonic acid is metabolized by either cyclooxygenase (resulting in the production of prostaglandins and thromboxane A_2) or lipoxygenase (eventually resulting in the production of leukotrienes). The effects of combined lipoxygenase and cyclooxygenase inhibition on HPV have been studied with BW755C and with nordihydroguaiaretic acid (NDGA). Both drugs have been extensively used in both in vitro and in vivo models. Four of five previous studies (20,22–25) examining the effects of BW755C on HPV have demonstrated either no effect or, in fact, potentiation of HPV. Potentiation of HPV with BW755C has generally been considered to be a consequence of inhibition of prostacyclin production. The present study is consistent with these prior reports that BW755C does not inhibit HPV. In the one study (20) in which BW755C inhibited HPV in the perfused rat lung, no effect was observed with 10 μM BW755C, a small but significant effect was observed with 100 μM BW755C, and complete inhibition of HPV was observed with 1000 μM BW755C. Because BW755C at concentrations of 1–10 μM can inhibit leukotriene synthesis, inhibition of HPV at high concentrations of BW755C may be due to a nonspecific effect of

Table 3. Effect of Leukotriene Synthesis Inhibitors, Leukotriene Receptor Antagonists, and Leukotriene Release Inhibitors on Hypoxic Pulmonary Vasoconstriction

Drug category	Drug	Reference	Species	Model	Effect on HPV
Combined lipoxygenase/ cyclooxygenase inhibitor	BW755C	Rubin (23)	Dog	Anesthetized	No effect
		Garrett (22)	Dog	Anesthetized	Potentiation
		Gottlieb (24)	Ferret	Perfused lung	No effect
		McCormack (25)	Pig	Anesthetized	Potentiation
		Marshall (20)	Rat	Perfused lung	Inhibition
	NDGA	Leffler (5)	Pig	Anesthetized	No effect
		Gottlieb (24)	Ferret	Perfused lung	No effect at appropriate concentration
Selective leukotriene synthesis inhibitor	DEC	Morganroth (11)	Rat	Perfused lung	Inhibition
		Morganroth (9)	Rat	Conscious	Inhibition
		Naeije (18)	Dog	Anesthetized	No effect
		Leffler (5)	Pig	Anesthetized	No effect
		Schuster (21)	Dog	Anesthetized	No effect
		Lonigro (26)	Dog	Anesthetized	No effect
	U60257	Morganroth (11)	Rat	Perfused lung	Inhibition
		Raj (14)	Sheep	Perfused lung	Inhibition
		McCormack (25)	Pig	Anesthetized	Nonspecific inhibition
Receptor antagonist	FPL55712	Morganroth (11)	Rat	Perfused lung	Inhibition
		Leffler (5)	Pig	Anesthetized	No effect
		Schuster (21)	Dog	Anesthetized	No effect
	FPL57231	Schreiber (13)	Sheep	Conscious	Inhibition
		Goldberg (15)	Pig	Anesthetized	Inhibition
		Leeman (16)	Dog	Anesthetized	Inhibition
		Raj (14)	Sheep	Perfused lung	Inhibition
		Ahmed (12)	Sheep	Conscious	Inhibition
		Kulik (27)	Sheep	Conscious	Nonspecific inhibition
Leukotriene release inhibitor	Cromolyn	Ahmed (17)	Sheep	Conscious	Inhibition
		Naeije (18)	Dog	Anesthetized	Inhibition
		Taylor (19)	Sheep	Conscious	Inhibition
		Ahmed (12)	Sheep	Conscious	Inhibition
		Pearl (28)	Sheep	Anesthetized	No effect
		Frantz (29)	Sheep	Conscious	No effect
		Hallemans (30)	Human	Conscious	No effect
		Howard (31)	Dog	Anesthetized	No effect

BW755C (37). Similarly, both studies of NDGA have shown no inhibition of HPV at appropriate concentrations of NDGA (5,24). Gottlieb et al. (24) demonstrated that NDGA could inhibit HPV at concentrations in excess of those required for cyclooxygenase and lipoxygenase synthesis inhibition, suggesting inhibition of HPV by a mechanism independent of the eicosanoid system.

The lipoxygenase pathway has been selectively inhibited with diethylcarbamazine (DEC) and U60257. Diethylcarbamazine primarily inhibits leukotriene A_4 synthesis (38). Four of six studies using DEC have demonstrated no effect on HPV (5,18,21, 26). The study by Lonigro et al. (26) demonstrated that hypoxia increases the levels of leukotriene C_4 and D_4 in bronchial lavage fluid. Diethylcarbamazine prevented the hypoxia-induced increase in leukotrienes but did not alter HPV. Two studies by Morganroth and coworkers (9,11) have demonstrated inhibition of HPV by DEC. One study demonstrated inhibition of HPV in a perfused rat lung model (11). In that study, dose-response curves indicated an ED_{50} of approximately 840 μg/mL, equivalent to 5.6 mM; concentrations of 100 μg/mL (670 μM) had no effect. In contrast, 5 μM DEC inhibits calcium ionophore-induced leukotriene B_4 and C_4 synthesis by 41% and 57% in murine mastocytoma cells, suggesting possible non-leukotriene-related effects in the perfused rat lung studies. Similarly, the in vivo rat studies of Morganroth et al. (9) used doses (100 mg/kg, IP) likely to produce plasma levels in the range of 100 mM (39), orders of magnitude in excess of the concentration required to inhibit leukotriene synthesis.

U60257, a 5′-lipoxygenase inhibitor, has been effective in inhibiting HPV in two perfused lung studies (11,14). Morganroth et al. (11) reported that 25 μg/mL (approximately 60 μM) was ineffective in inhibiting HPV but that doses of 56.6 and 143 μg/mL partially inhibited HPV. Raj and Chen (14) used perfusate concentrations of 200–500 μg/mL (approximately 0.5–1 mM) to inhibit HPV. However, the 50% inhibitory dose of U60257 for leukotriene synthesis is 4.6 μM and concentrations of 47 μM completely inhibit leukotriene formation (40); similarly, the IC_{50} for inhibition of ionophore-induced leukotriene release is 0.1 μM (25). The use of U60257 concentrations significantly above the range that inhibits leukotriene synthesis suggests non-leukotriene-related effects. McCormack and Paterson (25) reported that 50 mg/kg U60257 inhibited HPV but also decreased the pulmonary pressor response to angiotensin II, again suggesting a non-leukotriene-mediated mechanism of action.

In the present study we noted no inhibition of HPV with the administration of 20 mg U60257 as an aerosol (2% for 5 min). U60257 as an aerosol has been effective in reducing airway reactivity. Johnson et al. (41) reported that 15 breaths of a 1% U60257 solution decreased ozone-induced methacholine hyperresponsiveness in primates. Inhalation of an aerosol of 10 mg U60257 in dogs markedly reduced the increases in pulmonary vascular resistance that otherwise occurred with venous air infusion (42). Exposure to a 0.01% aerosolized solution for 3 min protected guinea pigs for the subsequent 1.5 h from antigen-induced bronchoconstriction (43). Similarly, 15 breaths of 0.01%–1.0% U60257 caused dose-dependent inhibition of lung resistance and compliance changes in rhesus monkey *Ascaris* reactors (44). The doses used in the present study in sheep were significantly higher than in these other studies and were probably effective in inhibiting leukotriene synthesis at the site or sites responsible for hypoxic pulmonary vasoconstriction.

The effects of leukotriene receptor blockers on HPV have been extensively studied (Table 3). Morganroth reported that 1 μg/mL FPL55712 inhibited HPV in the perfused rat lung (11). In contrast, the IC_{50} value for FPL55712 against slow-reacting substance of anaphylaxis is 0.005 μg/mL (45). FPL55712 did not inhibit HPV in two in vivo studies (5,21). In the study by Leffler et al. (5), the FPL55712 dose used was able to inhibit the responses to exogenous leukotriene C_4 and D_4 by 88% and 97%, respectively, but did not inhibit HPV.

The leukotriene receptor antagonist FPL57231 has consistently inhibited HPV in six studies (12–16,27). Raj and Chen (14) studied the effects of FPL57231 on HPV in isolated lamb lungs using a concentration of approximately 200 μg/mL. This concentration is not only markedly higher than the IC_{50} of FPL57231 for leukotriene D_4 (0.033 μg/mL) and slow-reacting substance of anaphylaxis (0.03 μg/mL) but also exceeds the IC_{50} for histamine (44 μg/mL), 5-hydroxytryptamine (10.8 μg/mL), and prostaglandin $F_{2\alpha}$ (12.3 μg/mL) (46). Thus, FPL57231 likely exerted non-leukotriene-mediated effects, a possibility supported by the finding that FPL57231 decreased baseline pulmonary vascular resistance by half. In vivo studies have used FPL57231 doses of 2 $mg \cdot kg^{-1} \cdot min^{-1}$ for 10 min (13), 1–4 $mg \cdot kg^{-1} \cdot min^{-1}$ for 10 min (15), 2 $mg \cdot kg^{-1} \cdot min^{-1}$ for more than 1 h (16), 2 $mg \cdot kg^{-1} \cdot min^{-1}$ for 17 min (12), and 0.2–2 $mg \cdot kg^{-1} \cdot min^{-1}$ for 15 min (27). There are no data on the plasma levels of FPL57231 with these infusion protocols. However, even with the assumption of complete metabolism on a single pass through the systemic circulation, a 2-$mg \cdot kg^{-1} \cdot min^{-1}$ infusion would result in pulmonary blood levels of approximately 30 μg/mL, again consistent with nonspecific effects. Gause et al. (47) demonstrated dose-dependent decreases in pulmonary vascular resistance with FPL57231 in the 1–10-mg/kg range in the fetal lamb using constant left pulmonary artery blood flow. These doses also decreased the pulmonary pressor responses to phenylephrine and to the thromboxane A_2 mimetic U46619, suggesting nonspecific effects of FPL57231. Reductions in pulmonary and systemic vascular resistance have been observed with FPL57231 in other studies (15,27,48).

Cromolyn sodium stabilizes mast cell membranes and may therefore prevent the release of leukotrienes (17,49). Cromolyn has been shown to inhibit HPV in conscious sheep (12,17,19) and anesthetized dogs (18). However, earlier studies demonstrated no inhibition with cromolyn (31), demonstrated variable effects of cromolyn (5), or demonstrated that the inhibitory effects of cromolyn were prevented by atropine pretreatment (51). Recent abstracts have demonstrated no inhibition of HPV with cromolyn in sheep (29) and humans (30). We have similarly demonstrated no effects of cromolyn in the halothane-anesthetized sheep model used in the current study (28). Overall, the cromolyn data suggest that hypoxia may cause mast cells to release modulators of pulmonary vascular tone (52) but that these modulators are not obligatory for hypoxic pulmonary vasoconstriction.

In the present study, LY171883 (30 mg/kg), a leukotriene D_4/E_4 antagonist (53), did not inhibit HPV. LY171883 has consistently been effective as a leukotriene antagonist in vitro and in vivo. Pretreatment of monkeys with 10 mg/kg of intravenous LY171883 inhibited hemodynamic responses to leukotriene D_4 administration (54). Pretreatment with 20 mg/kg of intravenous LY171883 prevented leukotriene C_4-induced constriction of arterioles in rat small bowel mesentery (55). Intravenous LY171883, 30 mg/kg, inhibited the systemic and regional hemodynamic effects of leukotriene D_4 and E_4 (56). Olson and Fleisher demonstrated that 10 mg/kg LY171883 completely inhibited the systemic and pulmonary hemodynamic responses to leukotriene C_4 and D_4 in the pig (57). Although LY171883 is more potent as a leukotriene D_4/E_4 antagonist than as a leukotriene C_4 antagonist, rapid metabolism of leukotriene C_4 to leukotriene D_4 may explain the in vivo efficacy of LY171883 against exogenously administered leukotriene C_4.

In summary, data are conflicting regarding the role of leukotrienes as mediators of HPV. Results with well-characterized synthesis inhibitors have been overwhelmingly negative with the exception of several studies that used DEC and U60257 at concentrations consistent with nonspecific results. Results with leukotriene receptor antagonists have generally shown inhibition of HPV but required drug concentrations orders of magnitude greater than needed for leukotriene receptor antagonism. Results with cromolyn have been variable and suggest that leukotrienes or other compounds may be released from mast cells and modulate rather than mediate the HPV response. In the current study, a cyclooxygenase/lipoxygenase inhibitor (BW755C), a leukotriene synthesis inhibitor (U60257), and a leukotriene end-organ antagonist (LY171883) did not alter the pulmonary pressor response to hypoxia in the halothane-anesthetized sheep. We therefore conclude that leukotrienes are not obligatory for hypoxic pulmonary vasoconstriction.

The writers thank Gail V. Benson for her technical assistance and Roz Mandell for her secretarial assistance.

References

1. Von Euler US, Liljestrand G. Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol Scand 1946;12: 301–20.
2. Fishman AP. Hypoxia on the pulmonary circulation. How and where it acts. Circ Res 1976;38:221–31.
3. Hales CA. The site and mechanism of oxygen sensing for the pulmonary vessels. Chest 1985;88:235S–40S.
4. Kadowitz PJ, Hyman AL. Analysis of responses to leukotriene D_4 in the pulmonary vascular bed. Circ Res 1984;55:707–17.
5. Leffler CW, Mitchell JA, Green RS. Cardiovascular effects of leukotrienes in neonatal piglets. Role in hypoxic pulmonary vasoconstriction? Circ Res 1984;55:780–7.
6. Yokochi K, Olley PM, Sideris E, Hamilton F, Huhanen D, Coceani F. Leukotriene D_4: a potent vasoconstrictor of the pulmonary and systemic circulations in the newborn lamb. Adv Prostaglandin Thromboxane Leukotriene Res 1982;9: 211–4.
7. Noonan TC, Kern DF, Malik AB. Pulmonary microcirculatory responses to leukotrienes B_4, C_4, and D_4 in sheep. Prostaglandins 1985;30:419–34.
8. Piper PJ, Letts LG, Galton SA. Generation of a leukotriene-like substance from porcine vascular and other tissues. Prostaglandins 1983;25:591–9.
9. Morganroth ML, Stenmark KR, Morris KG, et al. Diethylcarbamazine inhibits acute and chronic hypoxic pulmonary hypertension in awake rats. Am Rev Respir Dis 1985;131:488–92.
10. Morganroth ML, Stenmark KR, Zirrolli JA, et al. Leukotriene C_4 production during hypoxic pulmonary vasoconstriction in isolated rat lungs. Prostaglandins 1984;28:867–78.
11. Morganroth ML, Reeves JT, Murphy RC, Voelkel NF. Leukotriene synthesis and receptor blockers block hypoxic pulmonary vasoconstriction. J Appl Physiol 1984;56:1340–6.
12. Ahmed T, Oliver W Jr. Does slow-reacting substance of anaphylaxis mediate hypoxic pulmonary vasoconstriction? Am Rev Respir Dis 1983;127:566–71.
13. Schreiber MD, Heymann MA, Soifer SJ. Leukotriene inhibition prevents and reverses hypoxic pulmonary vasoconstriction in newborn lambs. Pediatr Res 1985;19:437–41.
14. Raj JU, Chen P. Role of eicosanoids in hypoxic vasoconstriction in isolated lamb lungs. Am J Physiol 1987;253:H626–33.
15. Goldberg RN, Suguihara C, Ahmed T, et al. Influence of an antagonist of slow-reacting substance of anaphylaxis on the cardiovascular manifestations of hypoxia in piglets. Pediatr Res 1985;19:1201–5.
16. Leeman M, Naeije R, Lejeune P, Mélot C. Influence of cyclooxygenase inhibition and of leukotriene receptor blockade on pulmonary vascular pressure/cardiac index relationships in hyperoxic and in hypoxic dogs. Clin Sci 1987;72:717–24.
17. Ahmed T, Oliver W Jr, Frank BL, Robinson MJ, Wanner A. Hypoxic pulmonary vasoconstriction in conscious sheep. Role of mast cell degranulation. Am Rev Respir Dis 1982;126:291–7.
18. Naeije R, Leeman M, Lejeune P. Effects of diethylcarbamazine and cromolyn sodium on hypoxic pulmonary vasoconstriction in dogs. Bull Eur Physiopathol Respir 1986;22:75–80.
19. Taylor BJ, Fewell JE, Kearns GL, Hill DE. Cromolyn sodium decreases the pulmonary vascular response to alveolar hypoxia in lambs. Pediatr Res 1986;20:834–7.
20. Marshall C, Kim SD, Marshall BE. The actions of halothane, ibuprofen and BW755C on hypoxic pulmonary vasoconstriction. Anesthesiology 1987;66:537–42.
21. Schuster DP, Dennis DR. Leukotriene inhibitors do not block hypoxic pulmonary vasoconstriction in dogs. J Appl Physiol 1987;62:1808–13.
22. Garrett RC, Foster S, Thomas HM III. Lipoxygenase and cyclooxygenase blockade by BW755C enhances pulmonary hypoxic vasoconstriction. J Appl Physiol 1987;62:129–33.
23. Rubin LJ, Hughes JD, Lazar JD. The effects of eicosanoid synthesis inhibitors on normoxic and hypoxic pulmonary vascular tone in dogs. Am Rev Respir Dis 1985;132:93–8.
24. Gottlieb JE, McGeady M, Adkinson NF Jr, Sylvester JT. Effects of cyclo- and lipoxygenase inhibitors on hypoxic vasoconstriction in isolated ferret lungs. J Appl Physiol 1988;64:936–43.
25. McCormack DG, Paterson NAM. The contrasting influence of two lipoxygenase inhibitors on hypoxic pulmonary vasocon-

striction in anesthetized pigs. Am Rev Respir Dis 1989;139: 100–5.

26. Lonigro AJ, Sprague RS, Stephenson AH, Dahms TE. Relationship of leukotriene C_4 and D_4 to hypoxic pulmonary vasoconstriction in dogs. J Appl Physiol 1988;64:2538–43.
27. Kulik TJ, Schutjer RK, Howland DF, Lock JE. Pulmonary and systemic vascular effects of SRS-A blockade in conscious lambs. Am J Physiol 1985;249:H968–73.
28. Pearl RG. Cromolyn sodium does not inhibit hypoxic pulmonary vasoconstriction in sheep. Anesth Analg 1990;71:83–7.
29. Frantz EG, Schreiber MD, Soifer SJ. Cromolyn sodium does not prevent hypoxia-induced pulmonary hypertension in newborn and young lambs. J Dev Physiol 1988;10:555–65.
30. Hallemans R, Mélot C, Naeije R, Dechamps P, Cailleau S. Cromolyn sodium does not inhibit hypoxic pulmonary vasoconstriction in normal man (abstract). Chest 1986;89:461S.
31. Howard P, Barer GR, Thompson B, Warren PM, Abbot CJ, Mungall IPF. Factors causing and reversing vasoconstriction in unventilated lung. Respir Physiol 1975;24:325–45.
32. Grover RF, Vogel JHK, Averill KH, Blount SG Jr. Pulmonary hypertension. Individual and species variability relative to vascular reactivity. Am Heart J 1963;66:1–3.
33. Heymann MA. Control of the pulmonary circulation in the perinatal period. J Dev Physiol 1984;6:281–90.
34. Unger M, Atkins M, Briscoe WA, King TKC. Potentiation of pulmonary vasoconstrictor response with repeated intermittent hypoxia. J Appl Physiol 1977;43:662–7.
35. Bjertnaes LJ, Hauge A, Nakken KF, Bredesen JE. Hypoxic pulmonary vasoconstriction: inhibition due to anesthesia. Acta Physiol Scand 1976;96:283–5.
36. Thilenius OG. Effect of anesthesia on response of pulmonary circulation of dogs to acute hypoxia. J Appl Physiol 1966;21: 901–4.
37. Hageman WE, Rose MP, Persico FJ. Antagonism by ETYA of the effects of leukotrienes on ileum and lung parenchymal strips independent of effects on arachidonic acid metabolism. Prostaglandins 1986;32:563–78.
38. Mathews WR, Murphy RC. Inhibition of leukotriene biosynthesis in mastocytoma cells by diethylcarbamazine. Biochem Pharmacol 1982;31:2129–32.
39. Edwards G, Awadzi K, Breckenridge AM, Gillies HM, Orme MLE, Ward SA. Diethylcarbamazine disposition in patients with onchocerciasis. Clin Pharmacol Ther 1981;30:551–7.
40. Bach MK, Brashler JR, Smith HW, Fitzpatrick FA, Sun FF, McGuire JC. 6,9-Deepoxy-6,9-(phenylimino)-$\Delta^{6,8}$-prostaglandin I_1 (U60257), a new inhibitor of leukotriene C and D synthesis: in vitro studies. Prostaglandins 1982;23:759–71.
41. Johnson HG, Stout BK, Ruppel PL. Inhibition of the 5-lipoxygenase pathway with piriprost (U60257) protects normal primates from ozone-induced methacholine hyperresponsive small airways. Prostaglandins 1988;35:459–66.
42. Domb M, Goldstein J, Vincent JL, et al. Haemodynamic, gasometric, and haematological effects of air infusion in dogs: leukotriene inhibition with U60257. Bull Eur Physiopathol Respir 1986;22:375–80.
43. Bach MK, Griffin RL, Richards IM. Inhibition of the presumably leukotriene-dependent component of antigen-induced bronchoconstriction in the guinea pig by piriprost (U60257). Int Arch Allergy Appl Immunol 1985;77:264–6.
44. Johnson HG, McNee ML, Bach MK, Smith HW. The activity of a new, novel inhibitor of leukotriene synthesis in rhesus monkey *Ascaris* reactors. Int Arch Allergy Appl Immunol 1983;70:169–73.
45. Augstein J, Farmer JB, Lee TB, Sheard P, Tattersall ML. Selective inhibitor of slow reacting substance of anaphylaxis. Nature 1973;245:215–7.
46. Sheard P, Holroyde MC, Ghelani AM, Bantick JR, Lee TB. Antagonists of SRS-A and leukotrienes. Adv Prostaglandin Thromboxane Leukotriene Res 1982;9:229–35.
47. Gause GE, Baker R, Cassin S. Specificity of FPL 57231 for leukotriene D_4 receptors in fetal pulmonary circulation. Am J Physiol 1988;254:H120–5.
48. Soifer SJ, Loitz RD, Roman C, Heymann MA. Leukotriene end organ antagonists increase pulmonary blood flow in fetal lambs. Am J Physiol 1985;249:H570–6.
49. Brogden RN, Speight TM, Avery GS. Sodium cromoglycate (cromolyn sodium): a review of its mode of action, pharmacology, therapeutic efficacy and use. Drugs 1974;7:164–282.
50. Kay GM, Grover RF. Lung mast cells and hypoxic pulmonary hypertension. Prog Resp Res 1975;9:157–64.
51. Rengo F, Trimarco B, Ricciardelli B, et al. Effects of disodium cromoglycate on hypoxic pulmonary hypertension in dogs. J Pharmacol Exp Ther 1979;211:686–9.
52. Ahmed T, Marchette B. Hypoxia enhances nonspecific bronchial reactivity. Am Rev Respir Dis 1985;132:839–44.
53. Fleisch JH, Rinhema LE, Haisch KD, et al. LY171883, 1-<2-hydroxy-3-propyl-4-<4-(1H-tetrazol-5-yl)butoxy>phenyl>ethanone, an orally active leukotriene D_4 antagonist. J Pharmacol Exp Ther 1985;233:148–57.
54. Hahn RA, MacDonald BR. Primate myocardial and systemic hemodynamic responses to leukotriene D_4: antagonism by LY171883. J Pharmacol Exp Ther 1987;242:62–9.
55. Michelassi F, Shahinian HK, Ferguson MK. Effects of leukotrienes B_4, C_4, and D_4 on rat mesenteric microcirculation. J Surg Res 1987;42:475–82.
56. Eimerl J, Sirén AL, Feuerstein G. Systemic and regional hemodynamic effects of leukotrienes D_4 and E_4 in the conscious rat. Am J Physiol 1986;251:H700–9.
57. Olson NC, Fleisher LN. Indomethacin and LY171883 modify porcine cardiopulmonary responses to leukotrienes. Prostaglandins Leukot Essent Fatty Acids 1989;35:175–82.

Effects of Sufentanil on Cerebral Blood Flow, Cerebral Blood Flow Velocity, and Metabolism in Dogs

Christian Werner, MD, William E. Hoffman, PhD, Verna L. Baughman, MD,
Ronald F. Albrecht, MD, and Jochen Schulte am Esch, MD

WERNER C, HOFFMAN WE, BAUGHMAN VL, ALBRECHT RF, SCHULTE AM ESCH J. Effects of sufentanil on cerebral blood flow, cerebral blood flow velocity, and metabolism in dogs. Anesth Analg 1991;72: 177–81.

The intracranial and systemic hemodynamic effects of sufentanil (20 μg/kg) were studied in 10 mongrel dogs. Baseline anesthesia was maintained with 0.7% end-tidal isoflurane and 50% nitrous oxide in oxygen. Catheters were inserted for blood pressure measurement, arterial and sagittal sinus blood sampling, radioactive microsphere injections, and intracranial pressure monitoring. Blood flow velocity was measured continuously in the middle cerebral artery using a transtemporal approach through a cranial window with a pulsed 8 MHz transcranial Doppler system (TCD). Cardiac output was measured using an electromagnetic flow probe on the pulmonary artery. After baseline measurements, sufentanil was injected and data were recorded at 5, 15, and 30 min. In group 1 (n = 5) blood pressure was not controlled, whereas in group 2 (n = 5) blood pressure was maintained at baseline levels with a phenylephrine infusion. Sufentanil decreased blood pressure from 120 ± 10 mm Hg (mean ± SEM) to 82 ± 11 mm Hg in group 1. Cardiac output decreased 40%–50% in both groups. Intracranial pressure did not change. Cerebral blood flow (CBF) and TCD blood flow velocity decreased significantly (35%–40%) with no difference between groups. Relative decreases in CBF and TCD blood flow velocity were closely correlated (r = 0.82). The cerebral hemodynamic changes were associated with a 35%–40% decrease in cerebral oxygen consumption. We conclude that sufentanil decreases CBF in response to decreased metabolic demand without significantly affecting intracranial pressure. Relative changes in CBF can be reproducibly monitored using TCD.

Key Words: ANESTHETICS, INTRAVENOUS—sufentanil. BRAIN, BLOOD FLOW, BLOOD FLOW VELOCITY, METABOLISM. MEASUREMENT TECHNIQUES, TRANSCRANIAL DOPPLER ULTRASONOGRAPHY.

Controversy exists regarding the effects of sufentanil on cerebral hemodynamics and intracranial pressure. Sufentanil has been reported to increase cerebral blood flow (CBF) without correlation to cerebral metabolism in dogs (1). Studies in patients and animals with reduced intracranial compliance have shown that sufentanil may also increase intracranial pressure (ICP) (2,3). In contrast, other studies have demonstrated that sufentanil either decreases or does not affect CBF or ICP (4–6).

In the present experiments we used transcranial Doppler sonography (TCD) to evaluate continuously cerebral hemodynamics after administration of sufentanil. In humans, noninvasive TCD measurements of blood flow velocity can be performed in the basal cerebral arteries such as the middle cerebral artery (MCA). Early reports indicate a high correlation among changes in CBF and CBF velocity during carotid endarterectomy, increased arterial blood pressure, and carbon dioxide-reactivity tests (7–9). However, it is unclear whether TCD monitoring accurately reflects changes in CBF during anesthesia.

The present experiments were performed (a) to measure the cerebrovascular effects of sufentanil in dogs anesthetized with isoflurane/nitrous oxide and (b) to correlate blood flow velocity in the MCA with CBF measured with radioactive microspheres.

Methods

These experiments were performed after approval from the Institutional Animal Care Committee. In 10

Received from the Departments of Anesthesiology, University of Illinois College of Medicine—Michael Reese Hospital, Chicago, Illinois, and University Hospital Eppendorf, Hamburg, Germany. Accepted for publication October 5, 1990.

Address correspondence to Dr. Werner, Department of Anesthesiology, University Hospital Eppendorf, Martinistrasse 52, 2000 Hamburg 20, Germany.

©1991 by the International Anesthesia Research Society

mongrel dogs (25–33 kg), anesthesia was induced with intravenous injection of thiamylal sodium and maintained with 1.4% end-tidal isoflurane and 50% nitrous oxide (N_2O) in oxygen after tracheal intubation. Paralysis was achieved by intravenous administration of vecuronium. Body temperature was measured using a rectal thermistor probe and was maintained constant at 38°C using a servocontrol heating pad. Heart rate (beats/min) was recorded with standard electrocardiography. Both femoral arteries and veins were catheterized for continuous measurement of mean arterial blood pressure (mm Hg), central venous blood pressure (mm Hg), and arterial blood samples. A thoracotomy was performed and a left atrial catheter was placed for microsphere injections to measure regional CBF. Cardiac output (L/min) was determined using an electromagnetic flow probe (Statham Gould) implanted on the left pulmonary artery. The skull of a dog, in contrast to that of a human, almost completely absorbs the emitted ultrasonic energy of a Doppler system. To achieve reproducible ultrasonic resolution in these experiments, the left zygomatic arch was resected, a cranial window was performed in the temporal bone, and the MCA was visualized. An 8-MHz ultrasonic probe was placed on the intact dura and fixed in a frame. Blood flow velocity (cm/s) was monitored continuously in the proximal MCA using a pulsed transcranial Doppler system (TC2-64 B, Eden Medical Electronics, Germany). Catheters were inserted via burr holes into the posterior sagittal sinus to obtain venous blood samples and into the lateral ventricle to measure intracranial pressure (ICP, mm Hg). At completion of surgery, isoflurane was adjusted to 0.7% end-tidal and the dogs were allowed a 45-min equilibration period.

The animals were randomly assigned to two groups for evaluation of cerebral hemodynamic and metabolic effects of sufentanil. In group 1 ($n = 5$) mean arterial blood pressure was not controlled after sufentanil administration, whereas in group 2 ($n = 5$) mean arterial blood pressure was maintained at control levels with a phenylephrine infusion. Measurements of regional CBF, TCD, ICP, cardiovascular parameters, and blood gas tensions were made before and 5, 15, and 30 min after intravenous injection of 20 μg/kg sufentanil.

Regional Cerebral Blood Flow Measurements

Regional CBF was measured four times in each animal using ^{57}Co, ^{113}Sn, ^{85}Sr, and ^{46}Sc labeled 15-μm microspheres (New England Nuclear). Stock solutions containing 500,000 microspheres/mL were suspended in isotonic saline with 0.05% Tween-80. Microspheres were vortexed for 1 min, and 5 mL was withdrawn (2.5×10^6 microspheres) and injected into the left atrium. The catheter was then flushed with saline. Starting 30 s before each microsphere injection and continuing for 90 s after each injection, blood was withdrawn from the femoral artery at 10 mL/min. The injections of microspheres were performed before and 5, 15, and 30 min after administration of sufentanil. At the end of the experiment the dog was killed by injection of 20% KCl, the brain was removed, and 1.5–3 g of tissue was dissected bilaterally from the following regions: cortex, caudate, cerebellum, fourth ventricular area, and pons/medulla. The activity of each microsphere in brain and blood samples was measured using a Nuclear Data 600 multichannel analyzer. Cerebral blood flow ($mL \cdot 100\ g^{-1} \cdot min^{-1}$) was calculated according to the methods of Heymann et al. (10) using the formula: CBF = (tissue activity/blood activity)·(withdrawal rate/tissue weight)·100.

Cerebral Oxygen Consumption

Arterial and sagittal sinus blood samples were taken after each CBF measurement for determination of blood gas tensions, pH, and oxygen content. Blood gas tensions were measured with an IL 1303 blood gas analyzer. Blood oxygen content was measured using an IL 282 cooximeter and was calculated by adding oxygen content to the oxygen dissolved in the plasma. Cerebral oxygen consumption ($CMRo_2$) ($mL\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$) was calculated by multiplying cortical CBF times the difference of femoral arterial and sagittal sinus oxygen content.

Transcranial Doppler Sonographic Blood Flow Velocity Measurements

Middle cerebral artery blood flow velocity was monitored continuously for correlation with cortical CBF using a pulsed 8-MHz transcranial Doppler ultrasound instrument (TC2-64 B, Eden Medical Electronics, Germany). The system operates with a maximum of 100-mW ultrasonic intensity at pulse repetition frequencies between 4.96 and 20.52 kHz. The ultrasonic focus is electronically adjustable in steps of 2.5 mm. The axial extension of the sample volume measures 10 mm according to a burst width of 13 μs. A high-pass filter of 150 Hz and a low-pass filter of 9 kHz are used for signal registration. Signals are computed using spectral analysis by 64-point Fast

Table 1. Hemodynamic Data and Intracranial Pressure Before and 5, 15, and 30 min After Administration of 20 μg/kg Sufentanil

	HR (beats/min)	MAP (mm Hg)	CVP (mm Hg)	CO (L/min)	ICP (mm Hg
Group 1 (n = 5)					
Baseline	147 ± 12	120 ± 10	5 ± 1	4.9 ± 0.3	16 ± 6
5 min	93 ± 20^a	87 ± 14^a	9 ± 3^a	3.4 ± 1.1^a	16 ± 6
15 min	90 ± 10^a	82 ± 14^a	9 ± 1^a	3.1 ± 0.8^a	15 ± 6
30 min	85 ± 7^a	82 ± 11^a	8 ± 1^a	3.1 ± 0.8^a	14 ± 5
Group 2 (n = 5)					
Baseline	146 ± 20	118 ± 24	7 ± 2	4.9 ± 0.9	21 ± 5
5 min	70 ± 7^a	118 ± 24	16 ± 1^{a,b}	2.4 ± 0.5^a	21 ± 4
15 min	75 ± 8^a	115 ± 21	13 ± 2^{a,b}	2.5 ± 0.5^a	20 ± 5
30 min	84 ± 10^a	119 ± 19	12 ± 1^{a,b}	2.3 ± 0.4^a	19 ± 6

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; CO, cardiac output; ICP, intracranial pressure.
Values are expressed as mean ± SEM.
$^a P < 0.05$ compared with baseline levels.
$^b P < 0.05$ compared with group 1 at each respective time level.

Fourier Transformation, averaging cycles of 4–20 s. The instantaneous systolic (V_{syst}, cm/s) and mean flow velocity (V_{mean}, cm/s) are digitally displayed in real-time after Doppler shift calculation and flow direction discrimination.

Statistics

Data are reported as mean ± SEM. All physiologic variables including CBF and TCD data were analyzed using a repeated measures analysis of variance comparing the two treatment groups over time. Significant changes from baseline levels and between groups were analyzed at each time period using Tukey post hoc tests. Pearson product moment correlations were made between changes in CBF and mean flow velocity relative to baseline values.

Results

Hemodynamic data and intracranial pressure before and after administration of sufentanil are shown in Table 1. Heart rate decreased significantly by 43% in both groups after sufentanil ($P < 0.05$). Mean arterial blood pressure decreased by 32% in group 1 and remained constant in group 2 (given phenylephrine). Central venous pressure increased above baseline levels (60%—85%) in both groups and was higher in group 2 than in group 1. Sufentanil significantly reduced cardiac output by 40%–50% in both groups. Intracranial pressure did not change in either group.

Blood gas tensions, pH, and TCD data are given i Table 2. Arterial oxygen and CO_2 tensions and p did not change significantly in either group ove time. Middle cerebral artery peak blood flow velocit (V_{syst}) did not change in group 1 but was significantl reduced 15 and 30 min after sufentanil in group ($P < 0.05$). Mean flow velocity (V_{mean}) decreased wit sufentanil in both groups ($P < 0.05$). In two animal (one dog in each group), sufentanil produced transient 30% increase in systolic and mean bloo flow velocity within 1–2 min, followed by a stead decline in TCD signals to values 25%–30% belo baseline 5 min after sufentanil.

Data for regional CBF and $CMRo_2$ are shown i Table 3. As indicated by analysis of variance, cortica and caudate blood flow and $CMRo_2$ decreased signif icantly after sufentanil administration in both group ($P < 0.05$). Because changes in CBF and V_{mean} wer similar in both groups after sufentanil, the group were combined and the data were presented a percent changes from baseline in Figure 1. Cerebra blood flow and V_{mean} decreased 30% after 20 μg/k sufentanil over the 30-min evaluation period. Th decrease in cortical CBF was closely correlated to th decrease in MCA blood flow velocity ($r = 0.82$).

Discussion

There is controversy concerning the effects of sufen tanil on CBF and ICP. In dogs, Milde et al. (1 observed a significant increase in CBF lasting fo 20 min and a transient increase in $CMRo_2$ wit administration of sufentanil in doses of 10–200 μg/kg

Table 2. Blood Gas Tensions, pH, and Transcranial Doppler Sonography Data Before and 5, 15, and 30 min After Administration of 20 μg/kg Sufentanil

	Po_2 (mm Hg)	Pco_2 (mm Hg)	pH	V_{syst} (cm/s)	V_{mean} (cm/s)
Group 1 ($n = 5$)					
Baseline	241 ± 9	33.6 ± 1.4	7.39 ± 0.02	43 ± 3	30 ± 2
5 min	246 ± 9	33 ± 1.2	7.36 ± 0.02	42 ± 3	21 ± 1[a]
15 min	242 ± 5	34 ± 0.6	7.36 ± 0.03	40 ± 2	20 ± 1[a]
30 min	235 ± 6	38.5 ± 3.2	7.34 ± 0.02	37 ± 2	19 ± 1[a]
Group 2 ($n = 5$)					
Baseline	225 ± 19	37.4 ± 1.1	7.39 ± 0.01	59 ± 4	41 ± 3
5 min	225 ± 18	38.2 ± 2.0	7.35 ± 0.01	50 ± 4	30 ± 4[a]
15 min	217 ± 24	38.5 ± 1.7	7.36 ± 0.02	47 ± 3[a]	29 ± 3[a]
30 min	216 ± 25	37.1 ± 1.3	7.35 ± 0.01	45 ± 3[a]	27 ± 3[a]

V_{syst}, systolic flow velocity; V_{mean}, mean flow velocity.
Values are expressed as mean ± SEM.
[a] $P < 0.05$ compared with baseline levels.

Table 3. Regional Cerebral Blood Flow (rCBF) and Cerebral Oxygen Consumption ($CMRo_2$) Before and 5, 15, and 30 min After Administration of 20 μg/kg Sufentanil

	rCBF					
	Cortex	Caudate	Cerebellum	Midbrain	Pons	$CMRo_2$
Group 1 ($n = 5$)						
Baseline	147 ± 20	120 ± 20	90 ± 10	105 ± 24	66 ± 10	6.2 ± 0.6
5 min	104 ± 18	86 ± 13	96 ± 17	104 ± 29	68 ± 16	3.9 ± 0.2[a]
15 min	103 ± 18	92 ± 14	99 ± 16	112 ± 29	83 ± 19	4.4 ± 0.3
30 min	97 ± 17	83 ± 14	96 ± 18	105 ± 29	71 ± 16	4.4 ± 0.2
Group 2 ($n = 5$)						
Baseline	129 ± 25	129 ± 20	90 ± 9	92 ± 9	61 ± 5	5.4 ± 0.7
5 min	89 ± 17	96 ± 12	71 ± 8	68 ± 11	44 ± 5	4.9 ± 0.3
15 min	77 ± 12	90 ± 11	109 ± 10	68 ± 9	49 ± 4	3.8 ± 0.3[a]
30 min	70 ± 7[a]	85 ± 14[a]	75 ± 16	66 ± 13[a]	50 ± 9	3.4 ± 0.5[a]

Values are expressed as mean ± SEM.
rCBF = $mL \cdot 100\ g^{-1} \cdot min^{-1}$; $CMRo_2$, $mL\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$.
[a] $P < 0.05$ compared with baseline levels.

The long-term increase in CBF after sufentanil did not correlate with either cerebral metabolic or blood pressure changes. In contrast, our results show that intravenous administration of 20 μg/kg sufentanil resulted in a significant decrease in CBF and CBF velocity along with a decrease in $CMRo_2$. Cerebral hemodynamic changes were independent of changes in arterial blood pressure and did not affect ICP. This agrees with studies in humans and rats that have shown a decrease or no change in CBF and $CMRo_2$ after sufentanil (4,5). It is unclear why Milde et al. (1) saw an increase in CBF with sufentanil, whereas our results and those of Keykhah et al. (4) show a decrease in CBF. One possible reason is the baseline anesthetic state before sufentanil was given. The dogs used by Milde et al. (1) were unanesthetized and paralyzed at the time baseline measurements were made before administration of sufentanil. The stress associated with unanesthetized paralysis may produce an increase in cerebrovascular resistance that is reversed by sufentanil. In a second series of dogs ($n = 3$), Milde et al. (1) ventilated the animals with 70% N_2O. They found an increase in baseline CBF and a subsequent decrease in CBF after sufentanil administration. This is consistent with the results of Keykhah et al. (4) who used 70% N_2O for baseline measurements in rats. It may be concluded that sufentanil consistently decreases CBF and $CMRo_2$ compared with N_2O or isoflurane plus N_2O used for baseline measurements.

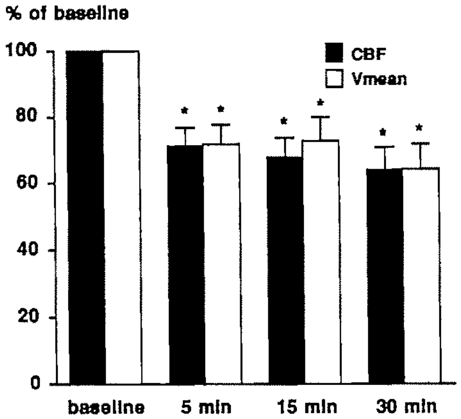


Figure 1. Cortical CBF and mean MCA blood flow velocity (V_{mean}) in all animals (n = 10) before and after 20 μg/kg sufentanil as percentages of baseline levels (*$P < 0.05$).

In previous studies, changes in flow velocity measured by TCD and CBF were correlated during carotid endarterectomy, angiotensin-induced arterial hypertension, and hypercapnia (7–9). In the present experiment we found a close correlation between MCA blood flow velocity and cortical CBF after sufentanil administration. However, some restrictions apply when interpreting TCD data. Doppler signals are sensitive to changes in the insonation angle and the diameter of the insonated vessel segment. This brings to question the validity of comparisons of baseline TCD measurements between animals. In addition, comparisons of TCD changes in each animal are possible over time only if the insonation angle and the depth of the ultrasonographic sample volume remain constant. To achieve an optimal signal in this study, we visualized the MCA and fixed the ultrasonic probe in a constant position. This allows comparison of TCD changes over time but comparison of baseline values are still questionable. The high correlation between CBF and TCD blood flow velocity also suggests that possible changes in the MCA diameter were no major factor in the present study. We conclude that TCD reproducibly measures relative changes in CBF during physiologic or drug challenges in the anesthetized subject.

In our studies, ICP was greater than expected in a nonpathological state. This may be the result of using N_2O for baseline anesthesia (11). Nitrous oxide can increase ICP due to increases in CBF (12) and cerebral blood volume (13). Increases in ICP have been shown after sufentanil administration in patients with reduced intracranial compliance (2,3). However, these results have been questioned by studies in patients with normal or increased ICP (6). Our results show that sufentanil did not increase ICP, even under conditions of relatively high baseline pressures.

In conclusion, this study shows that sufentanil decreases both CBF and MCA blood flow velocity in dogs anesthetized with isoflurane and N_2O without effect on ICP. The decrease in cerebral hemodynamics is not related to changes in blood pressure but is correlated with a reduction in $CMRo_2$. The close correlation between changes in CBF and blood flow velocity suggests the potential use of TCD in the continuous monitoring of changes in CBF in the anesthetic state.

The authors thank Richard Ripper and George Dominguez for their technical assistance.

References

1. Newberg Milde L, Milde JH, Gallagher WJ. Effects of sufentanil on cerebral circulation and metabolism in dogs. Anesth Analg 1990;70:138–46.
2. Marx W, Shah N, Long C, et al. Sufentanil, alfentanil and fentanyl: impact on cerebrospinal fluid pressure in patients with brain tumors. J Neurosurg Anesth 1989;1:3–7.
3. Newberg Milde L, Milde JH. Cerebral effects of sufentanil in dogs with reduced intracranial compliance. Anesth Analg 1989;68:S196.
4. Keykhah MM, Smith DS, Carlsson C, Safo Y, Englebach I, Harp JR. Influence of sufentanil on cerebral metabolism and circulation in the rat. Anesthesiology 1985;63:274–7.
5. Weinstabl C, Mayer N, Spiss CK, Podreka I. Indifferent effect of sufentanil on cerebral blood flow in human volunteers. Anesthesiology 1989;71:A106.
6. Mayer N, Weinstabl C, Richling B, Czech T, Spiss CK. Impact of sufentanil on intracranial dynamics in neurosurgical ICU patients. Anesthesiology 1989;71:A1138.
7. Halsey JH, McDowell HA, Gelmon S, Morawetz RB. Blood flow velocity in the middle cerebral artery and regional cerebral blood flow during carotid endarterectomy. Stroke 1989;20:53–8.
8. Werner C, Kochs E, Möllenberg O, Schulte am Esch J. The effects of angiotensin-induced arterial hypertension on canine cerebral blood flow velocities in correlation to cerebral blood flow. Anesth Analg 1990;70:S431.
9. Bishop CCR, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke 1986;17:913–5.
10. Heymann MA, Payne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 1977;20:55–79.
11. Sakabe T, Kuramoto T, Inoue S, Takeshita H. Cerebral effects of nitrous oxide in the dog. Anesthesiology 1978;48:195–200.
12. Hansen TD, Warner DS, Todd MM, Vust LJ. Effects of nitrous oxide and volatile anaesthetics on cerebral blood flow. Br J Anaesth 1989;63:290–5.
13. Archer DP, Labrecque P, Tyler JL, Meyer E, Trop D. Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. Anesthesiology 1987;67:642–8.

ANESTH ANALG
1991;72:182–6

Respiratory Effects of Spinal Anesthesia: Resting Ventilation and Single-Breath CO_2 Response

Richard A. Steinbrook, MD, and Mercedes Concepcion, MD

STEINBROOK RA, CONCEPCION M. Respiratory effects of spinal anesthesia: resting ventilation and single-breath CO_2 response. Anesth Analg 1991;72:182–6.

The effects of spinal anesthesia with bupivacaine or lidocaine on resting pulmonary ventilation and on the response to the single-breath carbon dioxide test were studied in 11 unpremedicated patients. Resting end-tidal P_{CO_2} *decreased from 34.8 ± 4.5 (mean ± SD) to 31.6 ± 4.6 mm Hg after induction of spinal anesthesia* ($P = 0.002$). *The decrease in end-tidal* P_{CO_2} *correlated negatively with patient age* ($r = -0.67$, $P = 0.02$) *and positively with spinal analgesic level* ($r = 0.58$, $P = 0.06$). *Breath-to-breath variability of ventilation increased during spinal anesthesia. Spinal anesthesia was not associated with statistically significant changes in tidal volume, respiratory rate, minute ventilation, mean inspiratory flow rate, inspiratory duty cycle duration, or the response to the single-breath* CO_2 *test.*

Key Words: ANESTHETIC TECHNIQUES, SPINAL. VENTILATION, SPINAL ANESTHESIA AND.

In previous studies, we have shown an increase in ventilatory responsiveness to carbon dioxide (CO_2) rebreathing during spinal anesthesia with bupivacaine (1) and tetracaine (2). We did not measure resting ventilation during those studies; spinal anesthesia is thought to have no significant effect on resting pulmonary ventilation (3). Nevertheless, we did observe a significant decrease in resting end-tidal partial pressure of CO_2 (P_{ETCO_2}) during tetracaine spinal anesthesia (2). The present study was designed to determine the effects of spinal anesthesia on resting ventilation and on the response to the single-breath (SB) CO_2 test. The SB_{CO_2} test is thought to be a measure of peripheral chemoreceptor sensitivity (4).

Methods

Eleven subjects, free of clinically significant cardiac or pulmonary disease, were studied. All were scheduled for lower extremity surgery and had agreed to have spinal anesthesia. The protocol was approved by the Human Subjects Committee of our institution. Written informed consent was obtained from each subject.

Subjects fasted overnight and received no preoperative medications. Baseline (prespinal) respiratory measurements were performed in the preoperative holding area less than 1 h before operation. Spinal anesthesia was administered in the operating room with standard technique, using 22- or 26-gauge spinal needles. After identification of the subarachnoid space, 2% lidocaine (70–80 mg, without glucose) or 0.5%–0.75% bupivacaine (15–23 mg, with or without glucose) was injected; the choice of local anesthetic was at the discretion of the clinician administering the anesthetic. The level of sensory anesthesia to pinprick was assessed every 5 min. When the level was unchanged on two successive determinations, respiratory measurements were repeated. No sedative medications were administered until completion of all respiratory measurements.

Respiratory measurements were made with the subjects supine, their heads supported by one or two pillows. Figure 1 shows a schematic representation of the apparatus. Subjects wore noseclips while breathing through a small rubber mouthpiece. Partial pressure of carbon dioxide (P_{CO_2}) was monitored continuously at the mouthpiece by mainstream infrared capnometry (Hewlett-Packard model 14360A in 10

Supported in part by BRSG S07 RR05950-04 awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health.

Received from the Department of Anesthesia, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. Accepted for publication October 6, 1990.

Address correspondence to Dr. Steinbrook, Department of Anesthesia, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

©1991 by the International Anesthesia Research Society

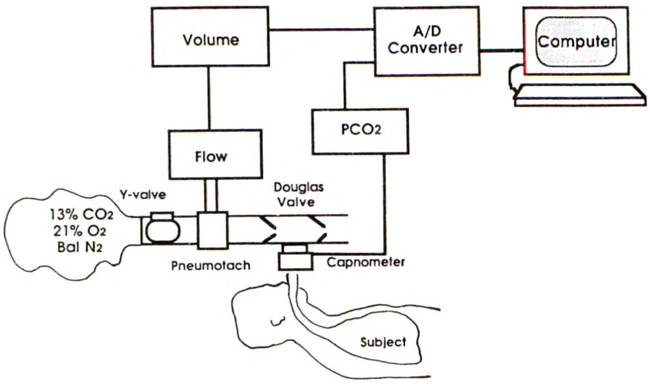


Figure 1. Diagram of experimental apparatus. Subjects breathed through a nonrebreathing (Douglas) valve. By turning a Y-valve, the investigator could substitute test gas (13% CO_2) for room air. The concentration of carbon dioxide (Pco_2) was measured continuously at the mouthpiece. Inspiratory volume was determined by integration of the flow signal from a pneumotachometer. The concentration of carbon dioxide and inspiratory volume data were stored by computer for later analysis.

subjects, Novametrix model 1260 in one subject). The capnometer was connected to a nonrebreathing valve (modified Douglas valve 21037, Warren E. Collins). Inspired gas volume was measured by integration (integrator amplifier model 13-4615-70, Gould) of the flow signal from a pneumotachometer (model 3813, Hans Rudolph, with variable reluctance pressure transducer model LCVR, range ± 2 cm H_2O, Celesco). A Y-valve allowed the investigator to substitute test gas (13% CO_2, 21% O_2, balance N_2) for room air. Inspiratory volume and airway Pco_2 signals were sampled at 10 Hz by a data acquisition system (Keithley System 570) and stored on a computer (Toshiba T3200) for later analysis.

The capnometer was calibrated before each set of respiratory measurements, using calibration cells provided by the manufacturer. Accuracy of calibration cell values was confirmed by capnometer measurement of analyzed calibration gases. The pneumotachometer was calibrated before each set of measurements with a 3-L syringe (Med Science).

Apparatus dead space (mouthpiece, capnometer cell, Douglas valve, plus connectors) was 80 mL. Inspiratory resistance of the breathing system was less than 2 mm Hg at 1 L/s.

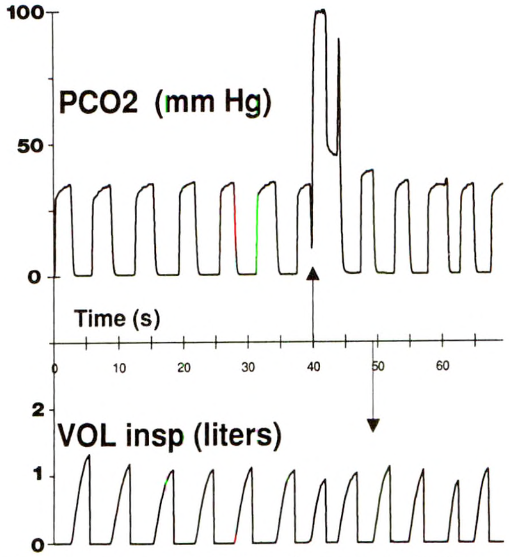


Figure 2. Computer record of data from a typical subject. After six breaths of room air, the subject inspired a single breath (*upward arrow*) of test gas, followed by five more breaths of room air. For each breath, end-tidal Pco_2, tidal volume, and inspiratory and expiratory times were measured; minute ventilation was calculated on a breath-by-breath basis. The breath with the greatest minute ventilation (*downward arrow*) was the response breath for calculation of the single-breath CO_2 response.

The SBco_2 test was performed as described by McClean et al. (4). After a 2–3-min period of quiet room air breathing through the breathing system, the subject was exposed to the test gas for a single tidal breath by turning the Y-valve during the expiratory phase of the previous breath. Because 13% CO_2 has a distinctive taste, no attempt was made to screen the subject's vision to prevent anticipation of the exposure. During the expiratory phase of the test breath, the Y-valve was turned back to the room air position, and the subject continued to breathe through the system. At least 3 min separated each exposure to the test gas. Each subject completed 5–8 SBco_2 tests before and 5–8 after administration of spinal anesthesia.

Data were acquired by computer over 50–70-s epochs. Each epoch included approximately 30 s of resting ventilation (i.e., 5–7 breaths of room air) and one SBco_2 test. Subjects usually breathed through the apparatus for the duration of the respiratory measurements (approximately 15–20 min). A typical record is shown in Figure 2.

For each breath, PETco_2 was determined as the maximal value of Pco_2 (except for the breath of test gas during the SBco_2 test as explained below). The inspiratory volume signal was analyzed to determine, for each breath, the tidal volume (VT), inspiratory time (TI), and expiratory time (TE). Total time (TTOT), respiratory frequency (f), inspiratory minute ventilation ($\dot{V}$I), mean inspiratory flow rate (VT/TI), and inspiratory duty cycle (TI/TTOT) were calculated on a breath-by-breath basis. Gas volumes are reported as measured (i.e., at ambient temperature and pressure, dry).

The SBco_2 response was calculated as described by McClean et al. (4). Control ventilation [$\dot{V}$I(C)] and control PETco_2 [PETco_2(C)] were determined as the average $\dot{V}$I and average PETco_2, respectively, for the five breaths immediately preceding the test breath. The response breath [$\dot{V}_I(S)$] was that breath with the greatest $\dot{V}_I$ within 20 s after the test breath. The stimulus P_{ETCO_2} [$P_{ETCO_2}(S)$] was the minimal P_{CO_2} for the test breath. Single-breath CO_2 response (in $L \cdot min^{-1} \cdot mm\ Hg^{-1}$) was calculated as the ratio of the difference in ventilation to the difference in P_{ETCO_2}:

$$SB_{CO_2}\ \text{response} = [\dot{V}_I(S) - \dot{V}_I(C)]/[P_{ETCO_2}(S) - P_{ETCO_2}(C)].$$

In the example shown in Figure 2, the test breath inspiration started at 39.7 s (upward arrow). For the five preceding breaths, P_{ETCO_2} was 35.0, 35.6, 35.2, 35.3, and 34.5 (average, 35.1) mm Hg, and the corresponding values of $\dot{V}_I$ were 11.4, 9.7, 10.6, 11.2, and 10.0 (average, 10.6) L/min. Stimulus P_{ETCO_2}, the minimal P_{CO_2} for the test breath, was 45.0 mm Hg (at 43.7 s). The response breath inspiration started at 49.2 s (downward arrow); $\dot{V}_I(S)$ was 13.4 L/min. Thus, in this example, the SB_{CO_2} response was $(13.4 - 10.6)/(45.0 - 35.1) = 0.28\ L \cdot min^{-1} \cdot mm\ Hg^{-1}$.

To determine the effects of spinal anesthesia on resting ventilation, mean values of all respiratory variables were compared before and after spinal anesthesia by paired *t*-tests; applying Bonferroni's correction for multiple comparisons would require $P < 0.008$ for statistical significance. Effects of intrathecal epinephrine were evaluated by unpaired *t*-tests on the mean values. Breath-to-breath variabilities before and after spinal anesthesia were compared by Wilcoxon signed rank tests on the coefficients of variation of the respiratory variables; the coefficient of variation is the standard deviation expressed as a percentage of the mean value. Correlations between patient age or anesthetic level and respiratory responses were by least-squares linear regression.

Results

Patient characteristics and drug dosages are shown in Table 1. The level of anesthesia to pinprick was between T-1 and T-11 in all subjects at the time of respiratory measurements. One patient (patient 4) received 0.4 mg intravenous atropine for bradycardia before completion of the postspinal respiratory measurements. All subjects tolerated the procedure well.

Compared with resting ventilation before administration of spinal anesthesia, respiration during spinal anesthesia was characterized by an average 9% decrease in P_{ETCO_2} and average 10% increases in $\dot{V}_I$ and V_T/T_I (Table 2). Although the magnitudes of the average changes are similar, the fall in P_{ETCO_2} is statistically significant ($P = 0.002$), whereas the increases in $\dot{V}_I$ and V_T/T_I are not ($P = 0.11$ and 0.06, respectively) because of the greater variability in these measures. Spinal anesthesia was not associated with significant changes in mean values of V_T, f, or T_I/T_{TOT}. Four patients received intrathecal epinephrine; as compared with the seven patients who did not, there were no significant differences in the respiratory changes associated with spinal anesthesia. Exclusion of data from the patient who received atropine did not change the statistical significance of the changes during spinal anesthesia.

Table 1. Patient Characteristics

Patient No.	Age (yr)	Sex	Height (cm)	Weight (kg)	Drug	Dose (mg)	Analgesic level
1	76	F	157	73	B[a]	15	T-2
2	57	F	168	64	B	15	T-4
3	39	M	170	77	B[a]	23	T-1
4	38	F	163	55	B	15	T-3
5	38	F	165	77	L[a]	70	T-4
6	74	F	163	71	B	15	T-11
7	41	M	175	82	L	80	T-7
8	77	F	173	55	B[a]	15	T-8
9	65	M	178	86	L	70	T-5
10	26	M	180	73	L	70	T-4
11	20	M	191	73	L	70	T-6

B, bupivacaine; L, lidocaine.
[a] With the addition of epinephrine, 0.2–0.3 mg.

Table 2. Effect of Spinal Anesthesia on Resting Ventilation

	Prespinal	Postspinal	*P*
P_{ETCO_2} (mm Hg)	34.8 ± 4.5	31.6 ± 4.6	0.002
V_T (mL)	780 ± 290	840 ± 210	0.24
f (breaths/min)	18.9 ± 4.7	18.7 ± 4.0	0.86
$\dot{V}_I$ (L/min)	13.7 ± 3.6	15.1 ± 4.5	0.11
V_T/T_I (mL/s)	630 ± 170	690 ± 210	0.06
T_I/T_{TOT}	0.37 ± 0.03	0.37 ± 0.03	0.85
SB_{CO_2} ($L \cdot min^{-1} \cdot mm\ Hg^{-1}$)	1.3 ± 1.1	0.9 ± 0.7	0.04

P_{ETCO_2}, end-tidal partial pressure of carbon dioxide; V_T, tidal volume; f, respiratory frequency; $\dot{V}_I$, minute ventilation; V_T/T_I, mean inspiratory flow rate; T_I/T_{TOT}, inspiratory duty cycle; SB_{CO_2}, single-breath CO_2 response.
Values are expressed as mean ± SD; $n = 11$.
P values were computed from paired *t*-tests.

We performed 146 SB_{CO_2} tests in the 11 patients—75 before and 70 during spinal anesthesia; of these, 139 were technically satisfactory. Unsatisfactory responses resulted from both investigator errors (i.e., turning the Y-valve during the wrong phase of respiration) and patient reactions (i.e., coughing or sighing). The response breath was usually, but not always, the breath immediately after the test breath. The mean SB_{CO_2} response decreased from 1.3 ± 1.1 before spinal anesthesia to 0.9 ± 0.7 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ ($P = 0.037$) during spinal anesthesia.

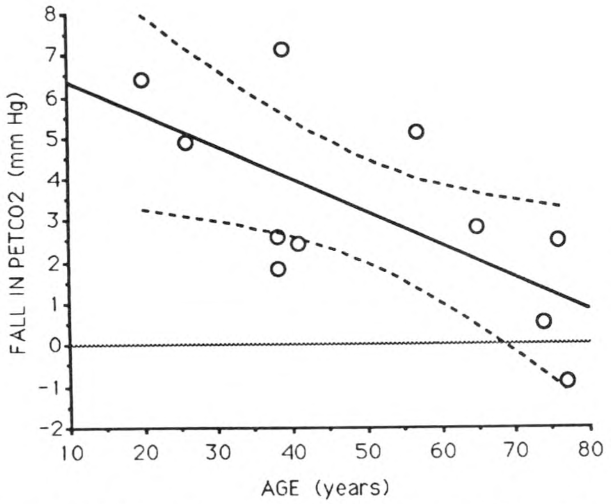


Figure 3. Fall in resting end-tidal Pco$_2$ (prespinal minus postspinal) versus patient age; r −0.67, $P = 0.02$. The regression line and 95% confidence limits are shown.

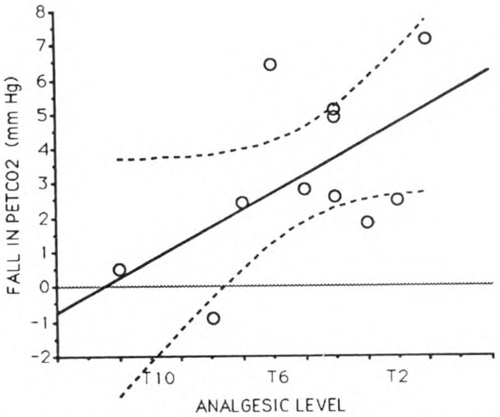


Figure 4. Fall in resting end-tidal Pco$_2$ (prespinal minus postspinal) versus analgesic level; $r = 0.58$, $P = 0.06$. The regression line and 95% confidence limits are shown.

Correlations of changes in resting PETCO$_2$ (prespinal minus postspinal) with patient age and analgesic level are shown in Figures 3 and 4. The magnitude of the decrease in PETCO$_2$ correlated negatively with patient age ($r = -0.67$, $P = 0.02$, Figure 3) and positively with analgesic level ($r = 0.58$, $P = 0.06$, Figure 4). There were significant correlations between the increase in $\dot{V}_I$ with patient age ($r = 0.76$, $P = 0.006$) and the increase in V_T/T_I with patient age ($r = 0.68$, $P = 0.02$).

Effects of spinal anesthesia on the coefficients of variation of the respiratory variables are shown in Figure 5. Breath-to-breath variability of ventilation increased during spinal anesthesia; the most significant increases were for respiratory frequency (18.1% to 25.6%, $P = 0.006$) and for inspiratory duty cycle (18.6% to 23.0%, $P = 0.006$).

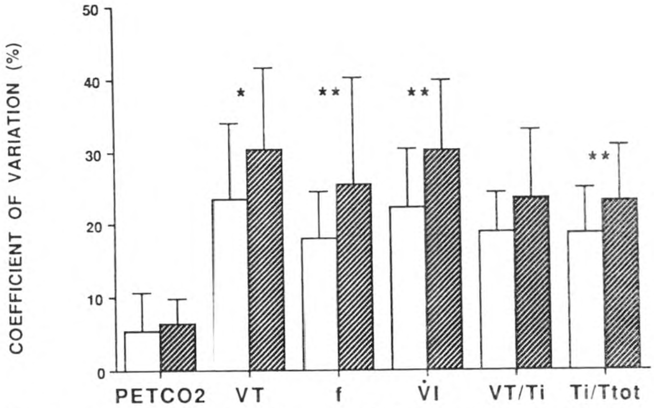


Figure 5. Variability of resting ventilation (coefficients of variation), prespinal (*open bars*) versus postspinal (*hatched bars*). The coefficient of variation is the standard deviation expressed as a percentage of the mean value. Error bars represent one standard deviation. $^*P < 0.05$; $^{**}P < 0.01$.

Discussion

Our observation of a decrease in resting PETCO$_2$ during spinal anesthesia is in agreement with our previous findings (2). A fall in PETCO$_2$ may represent either an alteration in ventilation-to-perfusion matching (i.e., increased dead space) or an increase in alveolar ventilation relative to CO$_2$ production (i.e., increased respiratory drive). Askrog et al. (5) also noted a decrease in arterial Pco$_2$ and a "slightly increased" minute ventilation in sedated subjects during tetracaine spinal anesthesia.

We have previously observed an increase in the ventilatory response to CO$_2$ rebreathing, a measure of central chemoreceptor drive, during spinal anesthesia (1,2). The single-breath CO$_2$ response was developed as a measure of peripheral chemoreceptor responsiveness (4). Our observation of no significant change in SBco$_2$ response during spinal anesthesia argues against peripheral chemoreceptor contribution to increased ventilatory drive associated with spinal anesthesia.

Ventilatory responses to hypoxia and hypercapnia are known to diminish with age in normal men (6). In a previous study (2) we found an inverse correlation between patient age and the magnitude of the increase with spinal anesthesia in minute ventilation during CO$_2$ rebreathing. In the present study, we observed an inverse correlation between age and the change in resting PETCO$_2$ (Figure 3), as well as positive correlations between age and the changes in resting $\dot{V}_I$ and V_T/T_I during spinal anesthesia, i.e., the youngest patients had the greatest decreases in PETCO$_2$ and the greatest increases in $\dot{V}_I$ and V_T/T_I.

Variability of ventilation during spinal anesthesia has not been reported previously. Indeed, there are few published studies on the normal variability of breathing. We observed significantly increased coefficients of variation for respiratory frequency, minute ventilation, and inspiratory duty cycle during spinal anesthesia. Spinal anesthesia-induced abdominal muscle paralysis increases chest wall compliance, reducing the mechanical load to breathing. Thus, our observation of increased variability of breathing frequency during spinal anesthesia is consistent with the findings of Daubenspeck (7) who noted reduced variability of breathing frequency in response to increased resistive loads. Cherniack and Longobardo (8) postulated that the respiratory control system may use fluctuations in breathing pattern to detect changes in mechanical characteristics of the lungs and chest wall.

Our observations of relatively low prespinal values for resting P_{ETCO_2} and relatively high prespinal values for V_T and $\dot{V}_I$ (Table 2) confirm the findings of Perez and Tobin (9) on the effects on breathing pattern of using a mouthpiece and noseclips. We cannot exclude the possibility that anxiety related to impending surgery contributed to the changes in ventilation in our patients. However, the correlation between the fall in P_{ETCO_2} and the level of spinal anesthesia (Figure 4) supports our hypothesis (1) that deafferentation of chest wall receptors may be responsible for the increased ventilation associated with spinal anesthesia, i.e., the higher the level of deafferentation, the greater the increase in ventilation and the greater the fall in P_{CO_2}.

In conclusion, spinal anesthesia in unsedated patients was associated with a 9% decrease in P_{ETCO_2} ($P = 0.002$) and with statistically insignificant increases in minute ventilation and mean inspiratory flow rate. Breath-to-breath variability of breathing increased with spinal anesthesia. Response to the SB_{CO_2} test, a measure of peripheral chemoreceptor function, decreased slightly during spinal anesthesia.

We are indebted to Ignatius Calalang, BS, BME, for help with computer programming, to E. John Orav, ScD, for statistical advice, and to Ellen Murray, RN, and Usha Dhingra, MD, for assistance in data acquisition and analysis.

References

1. Steinbrook RA, Concepcion M, Topulos GP. Ventilatory responses to hypercapnia during bupivacaine spinal anesthesia. Anesth Analg 1988;67:247–52.
2. Steinbrook RA, Topulos GP, Concepcion M. Ventilatory responses to hypercapnia during tetracaine spinal anesthesia. J Clin Anesth 1988;1:75–80.
3. Greene NM. Physiology of spinal anesthesia. 3rd ed. Baltimore: Williams & Wilkins, 1981:147–60.
4. McClean PA, Phillipson EA, Martinez D, Zamel N. Single breath of CO_2 as a clinical test of the peripheral chemoreflex. J Appl Physiol 1988;64:84–9.
5. Askrog VF, Smith PC, Eckenhoff JE. Changes in pulmonary ventilation during spinal anesthesia. Surg Gynecol Obstet 1984; 119:563–7.
6. Kronenberg RS, Drage CW. Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. J Clin Invest 1973;52:1812–9.
7. Daubenspeck JA. Influence of small mechanical loads on variability of breathing pattern. J Appl Physiol 1981;50:299–306.
8. Cherniack NS, Longobardo GS. Abnormalities in respiratory rhythm. In: Fishman AP, ed. Handbook of physiology. Section 3. The respiratory system. Volume 2. Control of breathing, Part 2. Baltimore: Waverly, 1986:729–49.
9. Perez W, Tobin MJ. Separation of factors responsible for change in breathing pattern induced by instrumentation. J Appl Physiol 1985;59:1515–20.

Saline-Filled Cuffs Help Prevent Laser-Induced Polyvinylchloride Endotracheal Tube Fires

Mitchel B. Sosis, PhD, MD, and Francis X. Dillon, MD

SOSIS MB, DILLON FX. Saline-filled cuffs help prevent laser-induced polyvinylchloride endotracheal tube fires. Anesth Analg 1991;72:187–9.

To determine whether the filling of tracheal tube cuffs with saline would decrease their combustibility during laser surgery, 20 polyvinylchloride tracheal tubes were studied. The cuffed end of each tracheal tube was inserted into the neck of an empty flask, and the tube and flask were flushed with oxygen for 5 min before cuff inflation. Ten tracheal tubes had their cuffs inflated with air, and 10 were inflated with saline. A Lasersonics LS880 CO_2 laser, set to 5 W for five of each of the two types of filled cuffs and to 40 W for the other pair of five tubes, was fired continuously at the cuffs for up to 1 min. No combustion occurred at the 5-W setting. The times to cuff perforation when the laser was set at 5 W were (mean ± SD) 1.00 ± 0.83 and 4.21 ± 3.91 s for the air- and saline-filled cuffs, respectively, a difference that was not statistically significant. The time to deflation of the saline-filled cuff (104.6 ± 67.5 s) was, however, significantly longer than that of the air-filled cuff (2.59 ± 1.97 s). When the tracheal tube cuffs were exposed to 40-W laser radiation, the cuff and adjacent tube shaft ignited in all cases when the cuffs were inflated with air, but only in one of five cases when the cuffs were filled with saline ($P < 0.05$). The filling of tracheal tube cuffs with saline provides simple, moderately effective partial protection of the cuff of endotracheal tubes during CO_2 laser airway surgery.

Key Words: EQUIPMENT, CUFFS—endotracheal. EQUIPMENT, LASERS—cuff flammability.

During laser airway surgery, the high energy of the laser is often employed in close proximity to combustible endotracheal tubes that may have anesthetic gases flowing through them that support combustion. Catastrophic tracheal tube fires have been reported under these conditions (1,2). These fires are the most common serious complication that occurs during CO_2 laser surgery of the airway (3). The incidence of such tracheal tube fires has been reported to be 0.57% (4).

Although the shafts of combustible endotracheal tubes can be protected from the CO_2 laser by techniques such as foil wrapping (5), the cuff still remains vulnerable to the laser's effects. LeJeune et al. (6) suggested that filling endotracheal tube cuffs with saline during laser surgery would prevent their combustion; however, they did not evaluate this possibility. This controlled study was designed to do so.

Methods

A Lasersonics (Santa Clara, Calif.) model LS880 CO_2 laser with a beam diameter of 0.68 mm in the continuous mode of operation was used. The cuffs attached to size 8.0-mm inner diameter polyvinylchloride endotracheal tubes (Mallinckrodt Hi-Lo; Argyle, N.Y.) were each inserted into the neck of an empty 250-mL Pyrex Ehrlenmeyer flask. A circle anesthesia system attached to an anesthesia machine was then connected to the endotracheal tube. Five liters per minute of oxygen flowed through the endotracheal tube and into the flask for 5 min. The tracheal tube cuff was then inflated to just seal at a pressure of 20 cm H_2O, which was maintained within the tracheal tube, flask, and anesthesia circuit by adjusting the pressure relief valve on the anesthesia machine. The laser beam was then directed perpendicularly at the part of the cuff that was protruding from the neck of the flask and that was, therefore, surrounded by air (see Figure 1). At a laser power of 5 W, the times to cuff perforation and loss of airway pressure were noted in 10 tracheal tube cuffs: five inflated with saline and five inflated with air. To study the combustibility of the tracheal tubes when their cuffs were inflated with saline or air, the laser's power was

---

Received from the Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; and the Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana. Accepted for publication September 7, 1990.

Address correspondence to Dr. Sosis, Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, 739 Jelke, 1753 West Congress Parkway, Chicago, IL 60612.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

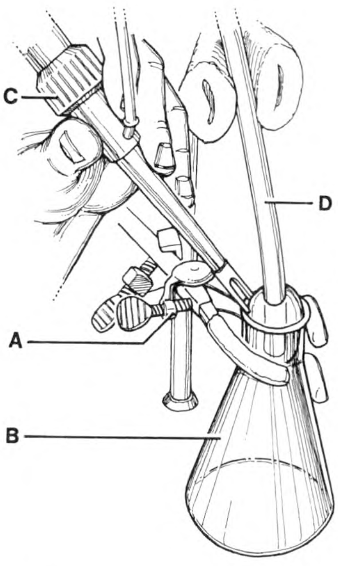


Figure 1. Diagram of the apparatus used to evaluate tracheal tube cuff flammability. A ring stand and clamp, *A*, support the Ehrlenmeyer flask, *B*, used during the trial. The laser handpiece, *C*, delivers CO_2 laser radiation from its console (not shown) toward a polyvinylchloride tracheal tube's cuff, *D*. The tracheal tube was connected to a circle anesthesia circuit and anesthesia machine, and the tracheal tube and flask had been flushed with oxygen for 5 min before inflation of the cuff with either saline or air.

Table 1. Time(s) to Cuff Perforation and Circuit Deflation (CO_2 laser set to 5 W)

Cuff	*n*	Perforation	Deflation
Air	5	1.00 ± 0.83	2.59 ± 1.97^a
Saline	5	4.21 ± 3.91^b	$104.6 \pm 67.5^{a,b}$

Values are mean ± SD.
[a] $P < 0.05$, paired Student's *t*-test, air versus saline.
[b] $P < 0.01$, paired Student's *t*-test, perforation versus deflation.

increased to 40 W; again, 10 tracheal tubes were studied, five with their cuffs filled with saline and five with air. The laser was actuated until combustion occurred or 1 min had elapsed.

Table 2. Incidence of Tracheal Tube Combustion (CO_2 laser set to 40 W)

Cuff	*n*	Combustion (%)
Air	5	100^a
Saline	5	20^a

[a] $P < 0.05$, Mann–Whitney U-test.

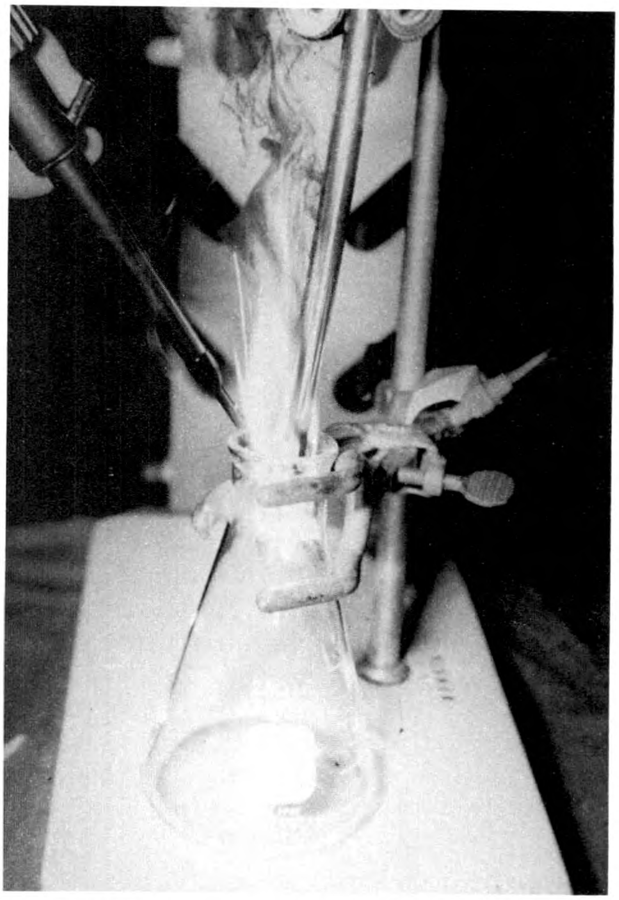


Figure 2. A CO_2 laser-induced fire involving the tracheal tube cuff and adjacent shaft is shown.

Results

Table 1 shows the times to cuff perforation and circuit deflation of endotracheal tubes with cuffs that were filled with air or saline. The saline-filled cuffs exposed to 5 W of continuous laser radiation were perforated in 4.21 ± 3.91 s (mean ± SD). This was not statistically different from the times necessary to perforate the air-filled cuffs (1.00 ± 0.83 s). However, because of the greater viscosity of water, leakage from the saline-filled cuffs was significantly slower than that of the air-filled cuffs; therefore, a longer interval elapsed before cuff leakage caused circuit decompression. When struck by the laser, deflation occurred after 2.59 ± 1.97 s in the air-filled endotracheal tube cuffs and after 104.60 ± 67.5 s in the tracheal tube cuffs filled with saline ($P < 0.05$). The deflation of the saline-filled cuff was significantly slower than its time to perforation. No combustion occurred during the trials at 5 W.

Table 2 shows the incidence of combustion with the laser set to 40 W. During all five trials with air-filled cuffs, combustion occurred after less than 1 s of laser discharge. Both the cuff and adjacent tracheal tube shaft were noted to be on fire (Figure 2). The saline-filled cuffs prevented laser-induced endotracheal tube explosions in all but one of the trials, during which the tube ignited in 5.19 s. The Mann–Whitney U-test was used to compare the incidence of flammability in the saline-filled and air-filled endotracheal tubes. It revealed a statistically significant difference at $P < 0.05$.

Discussion

The high-energy density of the laser combined with its proximity to combustible endotracheal tubes and their cuffs during laser airway surgery has resulted in serious airway fires (1,2). Such tracheal tube fires are the most common serious complication of laser airway surgery (3). The incidence of such fires was found to be 0.57% (4), making it one of the most common serious complications encountered in clinical anesthesia.

The shafts of combustible endotracheal tubes can be protected from the CO_2 laser by techniques such as foil wrapping with the correct metallic tape. Venture 1-mil copper or 3M No. 425 aluminum foil tape, for example, will protect polyvinylchloride tracheal tubes from 1 min of continuous CO_2 laser output at 70 W (5). The cuffs of endotracheal tubes, however, are thin and remain vulnerable to the effects of the laser beam, which may be directed at them during laryngologic surgery, because they cannot be protected with foil tape. The fact that the laser beam is often aligned along the axis of an operating laryngoscope during laryngeal surgery predisposes to its impingement on the cuff. Furthermore, the cuffs provide a large target because undersized tracheal tubes are often used during airway surgery to provide better exposure of the larynx for the surgeon, and because a large cuff is, therefore, necessary to assure a seal.

It has previously been suggested that filling tracheal tube cuffs with saline will protect them from the CO_2 laser because impingement of the laser beam onto the cuff will result in a jet of water that will act as a "built-in fire extinguisher." The saline should also act as a heat sink (6); however, this suggestion has not been previously tested. In the present study, cuff perforation by the CO_2 laser set to 5 W was not inhibited by saline filling; however, the saline-filled cuffs, although perforated by the laser beam as rapidly as air-filled cuffs, were significantly slower to deflate, allowing more time before reaching the point when airway pressure could no longer be maintained. The use of saline-filled cuffs prevented endotracheal tube ignition by the CO_2 laser set to 40 W in a statistically significant number of cases when compared with the control group of air-filled cuffs. Saline filling of the cuffs is, therefore, recommended for laser airway surgery. It is also suggested that a small amount of dye, such as methylene blue, be added to the saline so that cuff perforation will be obvious to the surgeon who will then immediately terminate operation of the laser. Further protection of the cuffs can be obtained by placing wet pledgets above them and keeping the pledgets moist throughout the procedure (7).

The assistance of Dr. Timothy Harwood in performing the statistical tests is gratefully acknowledged.

References

1. Cozine K, Rosenbaum LM, Askanazi T, Rosenbaum SH. Laser-induced endotracheal tube fire. Anesthesiology 1981;55:583–5.
2. Sosis M. Airway fire during CO_2 laser surgery using a Xomed laser endotracheal tube. Anesthesiology 1990;74:747–9.
3. Fried MP. Complications of CO_2 laser surgery of the larynx. Laryngoscope 1983;93:275–8.
4. Snow JC, Norton ML, Saluja TS, Estanislao AF. Fire hazard during CO_2 laser microsurgery on the larynx and trachea. Anesth Analg 1976;55:146–7.
5. Sosis M. Evaluation of five metallic tapes for protection of endotracheal tubes during CO_2 laser surgery. Anesth Analg 1989;68:392–3.
6. LeJeune FE Jr, LeTard F, Guice C, Marice A. Heat sink protection against lasering endotracheal cuffs. Ann Otol Rhinol Laryngol 1982;91:606–7.
7. Ohashi N, Asai M, Veda S, Imamura J, Wantanabe Y, Mizukoshi K. Hazard to endotracheal tubes by CO_2 laser beam. ORL (Oto-Rhino-Laryngol) (Basel) 1985;47:22–5.

ANESTH ANALG
1991;72:190-3

Effect of Intraoperative Analgesic Therapy on End-Expired Concentrations of Halothane Associated With Spontaneous Eye Opening in Children

Mehernoor F. Watcha, MD, Richard G. Lagueruela, MD, and Paul F. White, PhD, MD

WATCHA MF, LAGUERUELA RG, WHITE PF. Effect of intraoperative analgesic therapy on end-expired concentrations of halothane associated with spontaneous eye opening in children. Anesth Analg 1991;72:190–3.

We studied 94 healthy ASA physical status I or II children to determine the end-expired concentration of halothane associated with eye opening on emergence from anesthesia, and to determine if parenteral opioid therapy or regional analgesia significantly altered this concentration. In our study, anesthesia was maintained with halothane in an air-oxygen mixture. After the surgical procedure was completed, the inspired concentration of halothane was adjusted to zero and the end-expired concentrations were permitted to decrease spontaneously. The end-expired concentration at which the child spontaneously opened his or her eyes was recorded. There were no statistically significant differences in the values of the end-expired halothane concentration at eye opening between patients in the control group, who did not receive any supplementation of halothane anesthesia, and patients in the groups that received either morphine supplementation or regional analgesia. These data suggest that analgesia and hypnosis (or loss of consciousness) occur by different mechanisms during halothane anesthesia in children.

Key Words: ANESTHETICS, VOLATILE—halothane. POTENCY, ANESTHETIC—MAC. ANESTHESIA, PEDIATRIC. ANALGESICS, MORPHINE.

Tracheal extubation at the conclusion of a surgical procedure is often delayed in pediatric patients until they open their eyes, to minimize the possibility of laryngospasm, hypoxemia, and bradycardia (1). Although the concentrations of various inhalation agents associated with eye opening are known in adults, such data are not available for children (2–4). Because the minimum alveolar concentration (MAC) of halothane that prevents movement with skin incision and the concentration that prevents airway responses to tracheal intubation in 50% of patients are different in children and in adults, it is possible that alveolar concentrations of halothane associated with eye opening will also differ in children and adults (5,6).

This study was designed to determine the end-expired concentration of halothane associated with spontaneous eye opening in children, and to determine if an analgesic dose of morphine or a local anesthetic given intraoperatively significantly altered this value.

Materials and Methods

After obtaining institutional review board approval and written informed consent from the parents or legal guardians, 94 healthy (ASA physical status I and II) children, aged 6 mo to 13 yr, who were scheduled for elective surgery under general endotracheal anesthesia, were studied. Children were excluded if they weighed less than 8 kg, if they had a history of prematurity or central nervous system disease, if they had received any drugs preoperatively, or if tracheal intubation was not indicated.

Patients were anesthetized with 66% nitrous oxide (N_2O) and 1%–3% halothane in oxygen, using a Bain modification of a Mapleson D circuit (in children weighing less than 10 kg) or a circle absorber. All patients underwent tracheal intubation facilitated with 0.5 mg/kg intravenous atracurium. Anesthesia was then maintained with halothane in an air-oxygen mixture. Patients were randomly assigned to one of three groups. The control group (group A) received

---

Received from the Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri. Accepted for publication September 7, 1990.

Address correspondence to Dr. Watcha, Department of Anesthesiology, Children's Hospital of St. Louis, P.O. Box 14871, 400 South Kingshighway, St. Louis, MO 63178.

©1991 by the International Anesthesia Research Society

no supplementation of halothane anesthesia. The remaining patients received either 0.1 mg/kg intravenous morphine (group B) or an appropriate regional block with 0.25% bupivacaine with epinephrine 1 in 200,000 (group C) before skin incision. In group C 93% (28 of 30) received a caudal epidural injection, and the remaining 7% received a brachial plexus block. The efficacy of the regional block was evaluated postoperatively by demonstrating a lack of response to toe or finger pinching in the caudal epidural or brachial plexus groups, respectively.

At the end of the surgical procedure neuromuscular blockade was reversed with 1.0 mg/kg intravenous edrophonium and 0.01 mg/kg intravenous atropine. Halothane was discontinued, and the circuit was flushed with high flow oxygen (8–10 L/min). A catheter was inserted into the tracheal tube until the hub fitted tightly at a modified elbow connector and the tip was within 1 cm of the distal end of the tracheal tube (6,7). The catheter was connected to the aspirating port of a mass spectrometer (Perkin-Elmer mass spectrometer MGA 1100, Perkin-Elmer, Pomona, Calif.) that had been calibrated with halothane and carbon dioxide gases with an accuracy of ±0.02% (Scott Medical Products, Plumsteadville, Pa.). Gas concentrations were measured at 30–45-s intervals. The end-tidal concentration when the patient first spontaneously opened his or her eyes was recorded as the awakening concentration. Eye opening was defined as opening for a minimum of 3 s. Brief fluttering of the eyelids was not considered to be eye opening.

For statistical analysis, patients in each group were subdivided into three age groups for which data on MAC are available from the anesthesia literature (5,6). These groups include the following age ranges: (a) 6 mo to 2.5 yr, (b) 2.6–6 yr, and (c) 6.1–13 yr. The mean differences in the concentration at eye opening in the various groups were compared by an unpaired Student's *t*-test with Bonferroni's correction for multiple comparisons and by a one-way analysis of variance. If the null hypothesis was rejected, a Scheffe's test was performed for multiple comparisons of individual group means. A P value <0.05 was considered significant.

Results

Demographic data are presented in Table 1. The number of patients in each subgroup was similar to that in other published studies in adults (2–4). There were no significant differences in age, body weight, or sex distribution for children in groups A, B, or C. The neural blockade was successful in all patients in group C. The time between discontinuation of N_2O and the measurements at awakening was at least 45 min, and the end-tidal N_2O concentration was zero in all patients at awakening.

For each group and subgroup, the mean halothane concentration (±SEM) at eye opening is presented in Table 2 along with the age-related MAC values previously determined by Gregory et al. (5). There were no significant differences in the mean concentration at eye opening between groups A, B, and C. The lack of a modifying effect of morphine analgesia or regional blockade on the halothane concentration at eye opening was also noted when the comparison was performed separately for each age group. In each of the three age ranges, the number of patients who opened their eyes at an end-tidal halothane concentration of 0.15% did not differ significantly in groups that did or did not receive supplementation of halothane anesthesia by morphine or a regional nerve block procedure (Fisher's exact test, P > 0.05).

Table 1. Distribution of Patients by Number and Age (mean ± SD) in Each Group and Subgroup

Age range (yr)	Anesthetic group			Total
	A	B	C	
0.5–2.0				
n	10	10	12	32
Age	1.0 ± 0.5	1.3 ± 0.4	1.2 ± 0.6	1.2 ± 0.5
2.1–6.0				
n	12	10	9	31
Age	4.6 ± 1.3	3.9 ± 1.2	4.2 ± 0.9	4.2 ± 1.1
6.1–13.0				
n	12	10	9	31
Age	10.2 ± 3.0	10.4 ± 2.7	8.3 ± 1.2	9.7 ± 2.6
Total				
n	34	30	30	94
Age	5.5 ± 4.3	5.1 ± 4.2	4.3 ± 3.1	5.0 ± 3.9
Sex (M/F)	19/15	18/12	22/8	59/35

Table 2. Comparison of the End-Expired Concentration Values at Eye Opening (mean ± SEM) and of MAC

Age range (yr)	End-tidal concentration at eye opening (%)			MAC[a] (%)
	Group A	Group B	Group C	
0.5–2.5	0.14 ± 0.01	0.13 ± 0.01	0.12 ± 0.01	0.97
2.6–6.0	0.15 ± 0.01	0.15 ± 0.02	0.14 ± 0.01	0.91
6.1–13.0	0.16 ± 0.01	0.17 ± 0.01	0.15 ± 0.01	0.87

Patients are grouped by age and by method of supplementation of halothane anesthesia.

[a] MAC values are from Gregory et al. (5).

Discussion

Our estimates of the concentration of halothane associated with eye opening in children were lower than the values previously obtained in adults (2,3). This is in contrast to estimates of MAC, which are higher in children than in adults (5). Several possible explanations are available for this discrepancy. First, we used spontaneous eye opening as the end point because some of the children studied were too small to respond to specific commands, including commands to open their eyes. In the studies by Stoelting et al. and by Gross and Alexander, end-expired concentrations were measured when eye opening occurred in response to commands (2,3). It is likely that spontaneous eye opening during emergence from inhalation anesthesia in adults would occur at lower anesthetic gas concentrations than eye opening in response to verbal commands.

Second, different responses were used as the end point in our study and the study by Gregory et al. (5). Studies on MAC involve the determination of a minimum concentration that will prevent a purposeful motor response to a supramaximal stimulus. Our study involved the determination of the maximum concentration that permitted a response (eye opening) in the absence of a stimulus. Data from one dose-response cannot be extrapolated to another response. Deady et al. studied the anesthetic potencies of nitrous oxide, halothane, isoflurane, and enflurane in mice using three different end points: (a) the righting reflex, (b) movement response to tail clamping, and (c) tail flick responses to a heat stimulus. The ratio between the ED_{50} value for one response and that for another varied with each agent, and the authors could not predict the anesthetic concentration for one end point from that for a different stimulus (8). The lack of correlation between the concentration of halothane at eye opening and age-related MAC values is also consistent with data from Stoelting et al., who did not find a higher value for the concentration at eye opening in younger adults compared with older patients (2).

Third, the relationship between the end-expired and the alveolar concentrations may be altered during the period of rapid shallow respirations noted during emergence from anesthesia in pediatric patients (9–13). With respiratory rates exceeding 40 breaths/min, the end-expired concentration from stored data in the multiplex time-shared mass spectrometer may be underestimated by 10%, while the error with "on-line" data is 5% (11,12). In addition, contamination of the end-expired sample from inspired gas, dead space gas, and gas from underperfused alveoli may have falsely decreased the end-expired values obtained during our studies (7,9–13). We minimized some of these potential errors by excluding patients weighing less than 8 kg, by obtaining expired samples from the distal end of the tracheal tube, and by using the "STAT" mode to obtain mass spectrometer readings at 30–45-s intervals (10–13).

Although systematic errors in gas sampling may be responsible for the lack of effect of age on the concentration at awakening in our study, these errors should not affect the conclusion that supplemental analgesic therapy does not affect the halothane concentration at eye opening. The same method of gas sampling was used in patients who did or did not receive supplemental morphine or regional analgesia. Previous studies in adults have suggested that pain from the operation did not appear to be an important stimulus to awakening (2). Gross and Alexander have demonstrated that intraoperative morphine did not alter the awakening concentration of isoflurane (3). The present study extends this finding to children receiving halothane. In addition, it provides data to suggest that regional neural blockade of painful impulses from an operative site may not alter the end-expired concentration at which eye opening occurs.

Although gross motor movement, coughing, retching, and breath-holding may occur during emergence from anesthesia, eye opening is the best sign of awakening in a patient whose age does not permit testing of responses to specific commands (1). If eye opening is accepted as a clear sign of awakening, our data may suggest that analgesia and loss of consciousness occur by different mechanisms during halothane anesthesia in children. This speculation is supported by the fact that patients can be free of pain but still conscious during high-dose opioid anesthesia (14).

In summary, we conclude that the concentration of halothane at which children spontaneously open their eyes is not affected by age, morphine, or local analgesia.

We thank the staff of the Children's Hospital for their patience during the study and gratefully acknowledge the secretarial assistance of M. Bicknell in the preparation of this manuscript.

References

1. Motoyama EK. Recovery from anesthesia. In: Motoyama EK, Davis PJ, eds. Smith's anesthesia for infants and children. 5th ed. St. Louis: CV Mosby, 1990:316.

2. Stoelting RK, Longnecker DE, Eger EI II. Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluroxene anesthesia: MAC awake. Anesthesiology 1970;33:5–9.
3. Gross JB, Alexander CM. Awakening concentrations of isoflurane are not affected by analgesic doses of morphine. Anesth Analg 1988;67:27–30.
4. Jones RM, Cashman JN, Eger EI II, Damask M, Johnson BH. Kinetics and potency of desflurane (I-653) in human volunteers. Anesth Analg 1990;70:3–7.
5. Gregory GA, Eger EI II, Munson ES. The relationship between age and halothane requirements in man. Anesthesiology 1969; 30:488–91.
6. Watcha MF, Forestner JE, Connor MT, et al. Minimum alveolar concentration of halothane for tracheal intubation in children. Anesthesiology 1988;66:412–6.
7. Quasha AL, Eger EI II, Tinker JH. Determination and application of MAC (review). Anesthesiology 1989;53:315–34.
8. Deady JE, Koblin DD, Eger EI II, Heavner JE, D'Aoust B. Anesthetic potencies and the unitary theory of narcosis. Anesth Analg 1981;60:380–4.
9. Eger EI II. Anesthetic uptake and action. Baltimore: Williams & Wilkins, 1973:236–7.
10. Badgwell JM, Heavner JE, May WS, Goldthorn JF, Lerman J. End-tidal pCO_2 monitoring in children ventilated with either a partial rebreathing or a non-breathing circuit. Anesthesiology 1987;66:405–10.
11. Ozanne GM, Young WG, Mazzei WJ, Severinghaus JW. Multipatient anesthetic mass spectrometry: rapid analysis of data stored in long catheters. Anesthesiology 1981;55:62–70.
12. Severinghaus JW. Monitoring anesthetic and respiratory gases. In: Blitt CD, ed. Monitoring in anesthesia and critical care medicine. New York: Churchill Livingstone, 1985:270.
13. Burrows FA. Physiologic dead space, venous admixture and the arterial to end-tidal carbon dioxide difference in infants and children undergoing cardiac surgery. Anesthesiology 1989;70: 219–25.
14. Mummaneni N, Rao TL. Awareness and recall with high dose fentanyl-oxygen anesthesia. Anesthesiology 1980;59:948–9.

Effects of Neuroleptic Agents on Rat Skeletal Muscle Contracture In Vitro

Charlene A. Hon, PhD, Dennis F. Landers, MD, PhD, and Anita A. Platts

HON CA, LANDERS DF, PLATTS AA. Effects of neuroleptic agents on rat skeletal muscle contracture in vitro. Anesth Analg 1991;72:194–202.

The purpose of this investigation was to examine and compare the effects of both in vivo pretreatment and in vitro treatment with the neuroleptic agents droperidol, haloperidol, and trifluoperazine on skeletal muscle contracture using an in vitro model. Strips of normal rat diaphragm were challenged with succinylcholine and halothane (halothane: 1% and 3%) subsequent to either in vitro administration (10–100 μM) or in vivo pretreatment (0.35–2.80 mg/kg) with droperidol, haloperidol, or trifluoperazine. After equilibration, maximum increases in tension were recorded and mean data analyzed by analysis of variance ($P < 0.05$). When either droperidol or trifluoperazine was administered in vivo, contracture values after exposure to succinylcholine and halothane were significantly decreased. After in vivo pretreatment with haloperidol or in vitro administration of droperidol, succinylcholine-induced contractures were significantly reduced; contractures subsequently induced by halothane did not significantly differ from that of controls. In vitro treatment with haloperidol and trifluoperazine, however, produced significant increases in tension in muscles exposed to succinylcholine and halothane. This study provides evidence that droperidol may be considered a safe anesthetic adjunct in malignant hyperthermia-susceptible patients, and, additionally, that caution should be exercised when interpreting results from studies in which contracture testing is performed on muscle from patients treated with neuroleptic agents.

Key Words: HYPERTHERMIA, MALIGNANT—droperidol. ANESTHETICS, INTRAVENOUS—droperidol.

Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle that is unpredictable and potentially fatal. Malignant hyperthermia is characterized by a sudden increase in body temperature, hypermetabolism, severe metabolic acidosis, and widespread skeletal muscle rigidity. The cause of MH appears to be an underlying disorder of skeletal muscle membrane that prevents regulation of myoplasmic calcium concentrations. Hyperthermic episodes occur when susceptible individuals are exposed to halogenated anesthetics, depolarizing muscle relaxants (1), or in some cases to physical stress (2). Diagnosis of susceptibility to MH is based on clinical presentation and confirmed by in vitro skeletal muscle contracture tests. In vitro testing has been used to screen for the contracture-inducing properties of a number of drugs including anesthetic agents.

The clinical presentation of anesthetic-induced MH is similar to neuroleptic malignant syndrome (NMS); however, the clinical course is slower and the central symptoms are more prominent in NMS (3). Neuroleptic malignant syndrome is characterized by hyperthermia, skeletal muscle rigidity, and autonomic dysfunction, and is a life-threatening complication after chronic administration of antipsychotic or neuroleptic drugs (4,5). The butyrophenone and phenothiazine classes of drugs are commonly implicated as causative agents in the NMS.

The pathophysiology of both MH and NMS is poorly understood; however, because muscle biopsy specimens from NMS patients exhibit an abnormal contracture response to halothane (6) and because both MH and NMS can be successfully treated with dantrolene, there is speculation that these syndromes share a common pathophysiology. These disorders could, however, result from different mechanisms that produce similar perturbation of cellular membranes with concomitant dysfunctional calcium movements. Results from a recent study suggested that calcium regulatory mechanisms in muscle from

---

Received from the Department of Anesthesiology, University of Nebraska Medical Center, Omaha, Nebraska. Accepted for publication September 28, 1990.

Address correspondence to Dr. Hon, Department of Anesthesiology, University of Nebraska Medical Center, 600 South 42nd Street, Omaha, NE 68198-4455.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

NMS-susceptible patients may be defective. Using Ca^{2+} selective microelectrodes, intracellular calcium levels in muscle from NMS survivors were found to be almost five times those in control subjects (7). Malignant hyperthermia and NMS have unique characteristics that distinguish one from the other. For example, MH is genetically linked, whereas NMS is not. The onset of NMS is slow compared with that of MH and may take days or weeks to develop, with recovery extending over a prolonged period even after discontinuation of drug therapy (8).

The butyrophenones, droperidol and haloperidol, were at one time considered to be protective for patients with MH (9,10) and have been shown to be protective for MH-susceptible swine subjected to halothane testing (11,12). Despite their structural similarity, droperidol and haloperidol have different clinical uses.

The present study was prompted by the paradoxical observations that haloperidol could be used successfully in vivo to treat MH-associated symptoms such as muscle cramps and fatigue without adverse side effects (10), but when administered in vitro haloperidol has been shown to potentiate skeletal muscle contractures in MH-susceptible swine (13) and humans (14). We were also puzzled by the fact that the structurally similar compound, droperidol, alleviated contractures in a similar in vitro preparation (14,15). Although haloperidol has structural similarity to droperidol, it also has similarities to the phenothiazine, trifluoperazine. Like haloperidol, trifluoperazine has been implicated as a causative factor in NMS, is a calmodulin inhibitor (16,17), and has been shown to potentiate skeletal muscle contracture in MH-susceptible swine (13). To examine these observations, an animal model was used and the butyrophenones, haloperidol and droperidol, and the phenothiazine, trifluoperazine, were administered either in vitro or as an in vivo pretreatment. The effectiveness of these agents in alleviating or exacerbating skeletal muscle contractures induced by succinylcholine and halothane in an in vitro preparation of rat diaphragm was then examined. To our knowledge, this is the first study to examine the effects of both in vivo and in vitro treatment with haloperidol, droperidol, or trifluoperazine on skeletal muscle contracture.

Methods

After obtaining approval of the institutional Animal Review Committee, unanesthetized male Sprague–Dawley rats (200–350 g) were killed by decapitation. The diaphragm was quickly excised and placed in Krebs' (37°C) solution through which oxygen and carbon dioxide (95:5) were constantly bubbled. Muscle strips were prepared and tested in vitro using previously published techniques (18). After the muscle strips were affixed to glass platinum electrodes and suspended in a tissue bath (Phipps and Bird, Richmond, Va.), they were adjusted to a resting tension of 1 g and directly stimulated supramaximally with 0.2 Hz (Grass Instruments, Quincy, Mass.). The responses of the muscle fiber bundles were recorded using force displacement transducers and a pen recorder. After a 30-min equilibration period, the muscle strips were exposed to 50 mM succinylcholine for 5 min. Halothane (1%) was then vaporized (Foregger 500) into the gas phase for 5 min, and for the final 5 min 3% halothane was added. The halothane concentration in the gas phase was confirmed with a Riker Keiki Portable Anesthetic Gas Indicator.

For in vitro experiments, haloperidol, droperidol, and trifluoperazine were injected into the muscle bath at final concentrations of 10, 25, 50, or 100 μM 2–5 min before the addition of succinylcholine. Other in vitro studies have employed these drugs at concentrations of 10 μM (droperidol and haloperidol) (14,15) and 50 μM (haloperidol and trifluoperazine) (13) using skeletal muscle from rats, humans, and swine. Two different solutions of haloperidol were used in in vitro studies—haloperidol injection as the lactate or powdered haloperidol (Sigma Chemicals, St. Louis, Mo.) dissolved in ethanol. Powdered haloperidol is not soluble in water; therefore, ethanol has been used as a solvent in in vitro contracture studies (14). To control for the effect of ethanol, ethanol alone was added to the muscle bath in final concentrations of 0.1%, 0.3%, and 1%, or equivalent to the amount used to dilute haloperidol to final concentrations of 10, 25, and 100 μM.

For in vivo studies, animals were injected subcutaneously with haloperidol (in ethanol), droperidol, or trifluoperazine at doses of 0.35, 0.70, 1.40, or 2.80 mg/kg 1 h before being killed. In a previous in vivo study, haloperidol (0.35, 0.70, and 1.40 mg/kg) was used as a pretreatment to determine its effect as a protective agent against the hyperpyrexia induced by 2,4-dinitrophenol (19).

Strips of diaphragm from animals that received no in vivo pretreatment and that were not exposed to haloperidol, droperidol, and trifluoperazine in vitro served as controls. The maximum increase in baseline tension was recorded for each experimental and control condition. The results were tabulated and expressed as the mean maximum tension developed. Each value in the tables represents the contracture

Table 1. Effects of Haloperidol on Skeletal Muscle Contracture

Concentration	Mean maximum tension (g) ± SEM after in vitro treatment with:			
Haloperidol[a] (in vitro) μM	HPD[c]	Sch[c]	1% Hal[c]	3% Hal[c]
0	0	0.21 ± 0.08	0.47 ± 0.13	0.64 ± 0.14
10	0	0.08 ± 0.09	0.86 ± 0.18	1.08 ± 0.23
25	0	0.36 ± 0.21	1.35 ± 0.54	1.61 ± 0.52
50	0.13	0.99 ± 0.52	2.14 ± 0.75	2.05 ± 0.46
100	0.63	1.86 ± 0.47	2.60 ± 0.79	2.12 ± 0.49
Haloperidol[b] (in vitro) μM	HPD[c]	Sch[c]	1% Hal[c]	3% Hal[c]
0	0	0.21 ± 0.08	0.47 ± 0.13	0.64 ± 0.14
10	0	0.37 ± 0.13	0.76 ± 0.24	0.97 ± 0.41
25	0.08	0.74 ± 0.21	1.04 ± 0.37	1.21 ± 0.40
50	0.93	1.95 ± 0.51	1.35 ± 0.69	1.11 ± 0.52
100	2.06	2.77 ± 0.75	1.62 ± 0.64	1.20 ± 0.62
Ethanol alone (in vitro)	Ethanol	Sch	1% Hal	3% Hal
1%	0.13	0.41 ± 0.19	0.48 ± 0.12	0.56 ± 0.27
Haloperidol (in vivo) mg/kg		Sch[c]	1% Hal	3% Hal
0		0.21 ± 0.08	0.47 ± 0.13	0.64 ± 0.14
0.35		0.13 ± 0.05	0.44 ± 0.21	0.54 ± 0.25
0.70		0.14 ± 0.04	0.37 ± 0.17	0.54 ± 0.19
1.40		0.13 ± 0.06	0.48 ± 0.32	0.65 ± 0.33
2.80		0.19 ± 0.08	0.55 ± 0.18	0.71 ± 0.24

HPD, haloperidol; Sch, succinylcholine; Hal, halothane.

[a] Haloperidol injection USP.

[b] Haloperidol dissolved in ethanol.

[c] Significant differences within these groups ($P < 0.05$).

response of 8–10 strips from at least four animals. The data were analyzed using one-way analysis of variance with statistical significance assumed with $P < 0.05$.

Muscle specimens that had been exposed to haloperidol (100 μM) alone, to succinylcholine and halothane alone, or to a combination of haloperidol, succinylcholine, and halothane (1% and 3%) were prepared for electron microscopic examination. Strips of muscle were removed from the muscle bath and immobilized on applicator sticks with silk suture. The muscle strips were then immersed in buffered 2.5% glutaraldehyde and fixed for 2 h at room temperature. After three buffer rinses, the specimens were postfixed in 1% osmium tetroxide for 1 h at room temperature. The strips of muscle were then removed from the applicator sticks, rinsed in buffer, and processed for electron microscopy using routine alcoholic dehydration followed by embedding in Spurr's low viscosity resin. Ultrathin sections were obtained with a MT-1 Porter-Blum ultramicrotome and mounted on nickel grids. The sections were stained with uranyl acetate and lead citrate and viewed on a Philips 201 transmission electron microscope.

Results

Generally, there were progressive increases in contracture values in control, in in vitro, and in in vivo pretreatment groups when skeletal muscle was exposed to succinylcholine followed by 1% and 3% halothane. When haloperidol was administered in vitro at concentrations greater than 25 μM, skeletal muscle contraction was induced before the addition of succinylcholine and halothane (Table 1). Haloperidol was the only drug of the three tested that, when added to the muscle bath, initiated skeletal muscle contracture. At all concentrations of haloperidol given in vitro, there were significant increases in contractures produced by succinylcholine and halothane (Table 1). The results using haloperidol dissolved in ethanol were similar to those of haloperidol as the lactate (injectable haloperidol) except that,

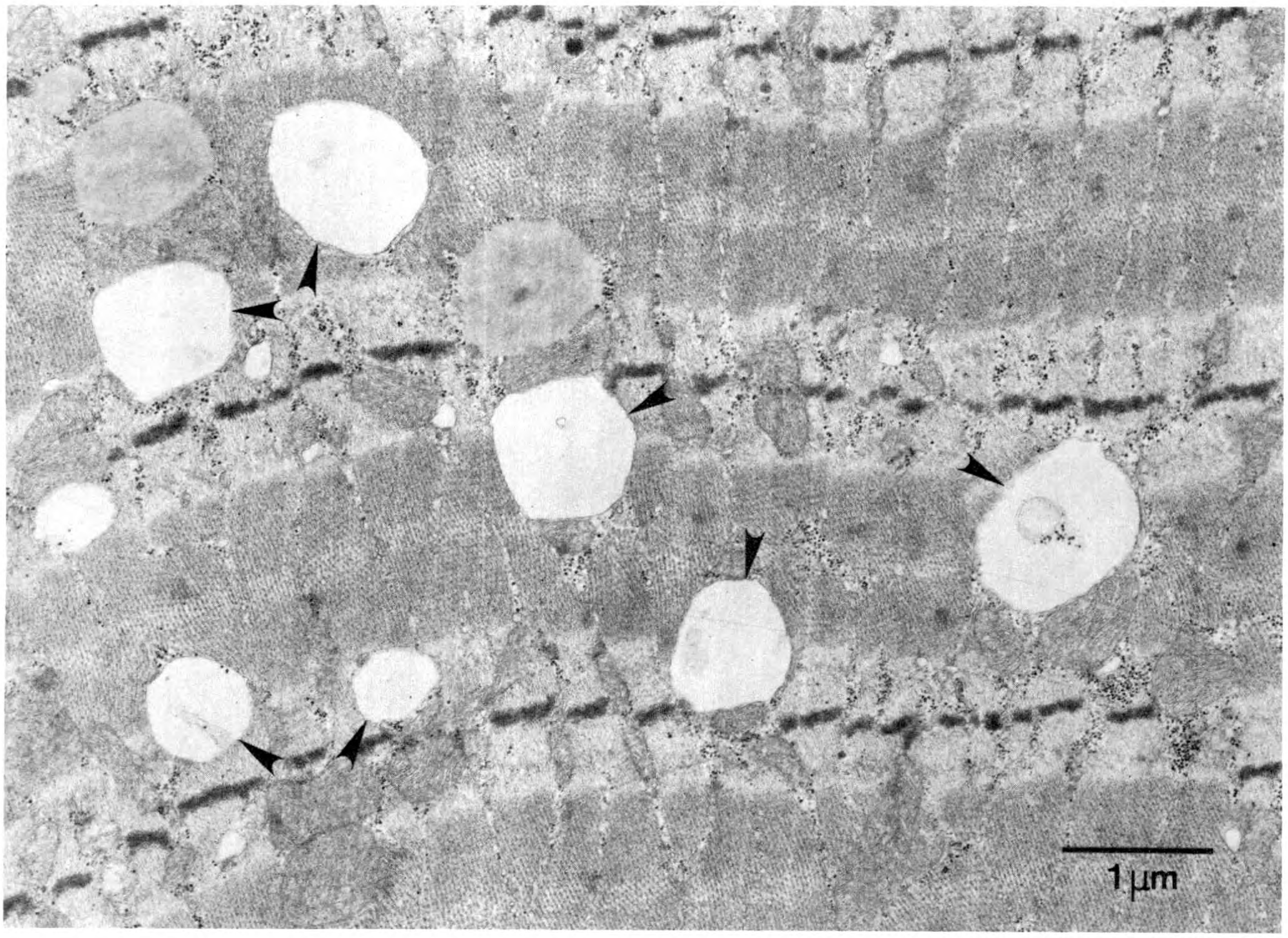


Figure 1. Numerous translucent, membrane-bound vesicles (*arrows*) were observed in rat diaphragm after haloperidol (100 µM) was added to the muscle bath (20,000×).

at a concentration of 25 µM, contractures were elicited in the absence of other triggering conditions, and contracture values decreased with the addition of 1% halothane when either 50 or 100 µM haloperidol in ethanol was given (Table 1). When ethanol alone at a final concentration of 1% was added to the muscle bath, skeletal muscle contraction was elicited in the absence of other triggering agents, and succinylcholine-induced contractures were significantly increased. Ethanol (1%) in the muscle bath is equivalent to the concentration that was used to dissolve haloperidol to a final concentration of 100 µM. At final bath concentrations of 0.1% or 0.3% ethanol, significant differences in contracture values from that of control specimens were not observed (data not shown).

Ultrastructural examination of myofibrils from muscle strips that had been exposed in vitro to haloperidol (100 µM) alone as well as in combination with either or both succinylcholine and halothane revealed the presence of large, translucent, membrane-bound vesicles (Figure 1) that were not observed in control specimens. When haloperidol was not present in the muscle bath, these vesicles were not observed. Disruption of the normal ultrastructure occurred in numerous myofibrils after exposure to succinylcholine and halothane. In addition, contraction bands were observed in some myofibrils (Figure 2).

The results of in vivo pretreatment with haloperidol were in contrast to the results obtained from in vitro exposure to this drug. When haloperidol was given as a pretreatment 1 h before killing the rats, a significant decrease in contracture values was observed in muscle exposed to succinylcholine. Although addition of 1% and 3% halothane to the muscle bath appeared to increase contracture values for muscle strips previously exposed to succinylcholine, these increases were not significantly different from control values (Table 1). The increase in contrac-

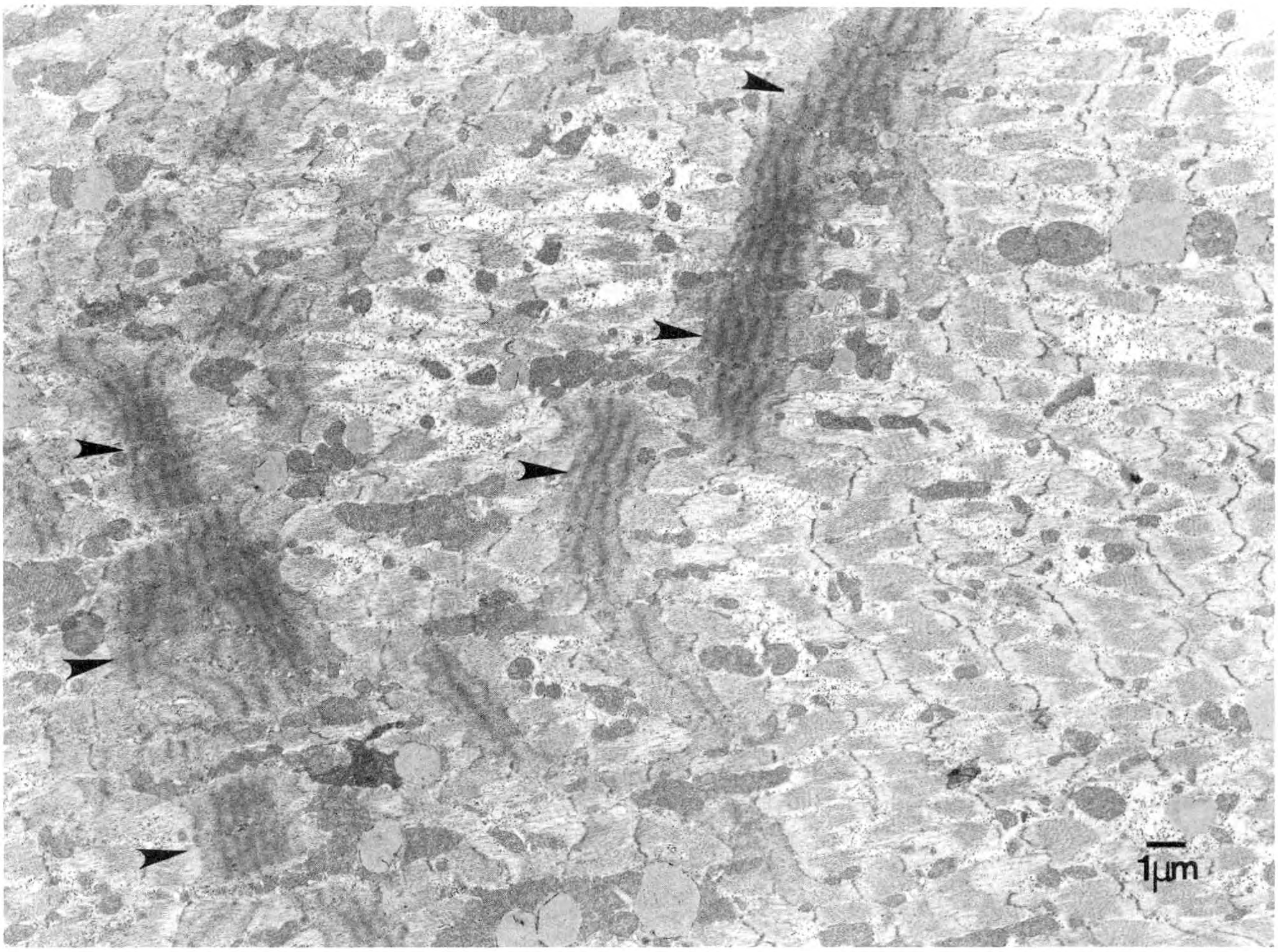


Figure 2. Contraction bands (*arrows*) were observed in some myofibrils; this specimen was obtained from a strip of diaphragm that was exposed to haloperidol (100 μM) for 2 min followed by succinylcholine (50 mM) for 5 min (5000×).

ture values observed after addition of halothane was significantly smaller when haloperidol was administered in vivo.

After in vitro treatment with the structurally similar butyrophenone, droperidol, succinylcholine-induced contractures were significantly reduced and contractures induced by halothane in muscle previously exposed to succinylcholine did not significantly differ from that of controls. At the highest concentration used in vitro (100 μM), contracture values for all triggering conditions were greater that those of controls. However, when these values were compared using Student's *t*-test, differences were not significant. When given as a pretreatment in vivo, droperidol significantly reduced contractures for all triggering conditions (Table 2).

Trifluoperazine alone did not induce skeletal muscle contracture when added in vitro but did significantly potentiate contractures when the muscle strips were exposed to succinylcholine followed by halothane (1% and 3%). When trifluoperazine was administered as an in vivo pretreatment, contractures produced by all triggering conditions were significantly reduced (Table 3).

Discussion

The purpose of this study was to examine and compare the effects of in vitro treatment and in vivo pretreatment with the neuroleptic agents haloperidol, droperidol, or trifluoperazine on skeletal muscle contracture using a rat diaphragm preparation as an in vitro animal model. When strips of diaphragm were sequentially exposed to succinylcholine, 1% halothane, and 3% halothane, there were progressive increases in contracture tension for both control and experimental groups; however, when haloperidol was used in vitro, contraction began before the addi-

Table 2. Effects of Droperidol on Skeletal Muscle Contracture

Concentration	Mean maximum tension (g) ± SEM after in vitro treatment with:			
Droperidol (in vitro) μM	DPD	Sch[a]	1% Hal	3% Hal
0	0	0.21 ± 0.08	0.47 ± 0.13	0.64 ± 0.14
10	0	0.15 ± 0.08	0.52 ± 0.19	0.69 ± 0.21
25	0	0.16 ± 0.09	0.42 ± 0.20	0.55 ± 0.26
50	0	0.19 ± 0.07	0.50 ± 0.24	0.61 ± 0.27
100	0	0.30 ± 0.18	0.58 ± 0.26	0.71 ± 0.25
Droperidol (in vivo) mg/kg		Sch[a]	1% Hal[a]	3% Hal[a]
0		0.21 ± 0.08	0.47 ± 0.13	0.64 ± 0.14
0.35		0.11 ± 0.06	0.29 ± 0.15	0.43 ± 0.15
0.70		0.12 ± 0.04	0.39 ± 0.12	0.51 ± 0.09
1.40		0.15 ± 0.07	0.30 ± 0.10	0.53 ± 0.18
2.80		0.18 ± 0.08	0.44 ± 0.15	0.62 ± 0.16

DPD, droperidol; Sch, succinylcholine; Hal, halothane.
[a] Significant differences within these groups ($P < 0.05$).

Table 3. Effects of Trifluoperazine on Skeletal Muscle Contracture

Concentration	Mean maximum tension (g) ± SEM after in vitro treatment with:			
Trifluoperazine (in vitro) μM	TFP	Sch[a]	1% Hal[a]	3% Hal[a]
0	0	0.21 ± 0.08	0.47 ± 0.13	0.64 ± 0.14
10	0	0.16 ± 0.05	0.57 ± 0.36	0.76 ± 0.24
25	0	0.29 ± 0.10	0.57 ± 0.21	0.97 ± 0.12
50	0	0.26 ± 0.11	0.78 ± 0.23	1.06 ± 0.24
100	0	0.21 ± 0.05	0.78 ± 0.22	0.97 ± 0.20
Trifluoperazine (in vivo) mg/kg		Sch[a]	1% Hal[a]	3% Hal[a]
0		0.21 ± 0.08	0.47 ± 0.13	0.64 ± 0.14
0.35		0.14 ± 0.06	0.37 ± 0.23	0.59 ± 0.25
0.70		0.08 ± 0.05	0.30 ± 0.09	0.46 ± 0.09
1.40		0.15 ± 0.10	0.44 ± 0.22	0.67 ± 0.27
2.80		0.15 ± 0.08	0.52 ± 0.19	0.68 ± 0.13

TFP, trifluoperazine; Sch, succinylcholine; Hal, halothane.
[a] Significant differences within these groups ($P < 0.05$).

tion of the triggering agents. The ability of succinylcholine and halothane to act synergistically to induce skeletal muscle contracture in isolated strips of rat diaphragm and human skeletal muscle has been reported previously (18,20). In the present study, only the effects of halothane on succinylcholine-induced contractures were examined. Conflicting results have been reported regarding the ability of succinylcholine to induce skeletal muscle contracture in both MH-susceptible humans and swine (20–25). However, the ability of halothane alone to induce contractures in MH-susceptible humans and swine is well documented. In the present study, halothane at concentrations of both 1% and 3% potentiated the contracture effects induced by succinylcholine.

Results of this study support the work of other investigations in which haloperidol in vitro potentiated skeletal muscle contractures (13,14). This study, however, extends those observations by providing data from a range of concentrations, and further, by comparing the effect of powdered haloperidol, which needs to be dissolved in ethanol, to haloperidol injection, which is water-soluble. Haloperidol injection, when added directly into the muscle bath over a range of concentrations (10–100 μM), potentiated skeletal muscle contractures. At concentrations greater than 25 μM, haloperidol in vitro induced skeletal muscle contracture in the absence of other agents, and succinylcholine-induced contractures were potentiated by the addition of 1% halothane.

When 3% halothane was added, however, contracture values decreased from values obtained after the addition of 1% halothane. Ultrastructural examination of muscle that was exposed to haloperidol alone or in combination with succinylcholine and halothane revealed the presence of large, translucent, membrane-bound vesicles (Figure 1) that were not observed in control specimens or in the absence of haloperidol. The vesicles appeared to be dilations of the sarcoplasmic reticulum. The reduction in tension that was observed when muscle was challenged with halothane after exposure to haloperidol (50 and 100 μm) and succinylcholine may be attributed to the disruption of the normal myofibrillar structure and the presence of contraction bands (Figure 2). Although the morphologic studies were not exhaustive and were strictly qualitative, these observations and those of other investigators suggest that, when given in vitro, haloperidol may have a direct effect on skeletal muscle. Haloperidol may act on the sarcoplasmic reticulum in a manner similar to halothane or caffeine to activate a calcium-induced calcium release mechanism (26).

Haloperidol (10 μM) dissolved in ethanol has been shown to augment succinylcholine-induced contractures in the presence of halothane (14). To determine the effect of ethanol on skeletal muscle contracture, ethanol alone was added to the muscle bath. Another study that used ethanol to dissolve butyrophenones reported that if the final concentrations of ethanol in the muscle bath exceeded 0.1%, skeletal muscle contractures were potentiated (14). In the present investigation, initiation and potentiation of skeletal muscle contraction was observed when the final bath concentration of ethanol was 1%. The results using haloperidol in ethanol were comparable to those obtained when injectable water-soluble haloperidol was employed (Table 1). However, the most notable exceptions were that contractures were much greater when haloperidol plus ethanol was added alone at concentrations of 25, 50, and 100 μM. At least some of the potentiating effect observed at high concentrations may be explained by the presence of ethanol in the muscle bath. The increase in resting tension that is produced by haloperidol and its ability to potentiate contractures produced by other triggering agents is presumably due to an increase in myoplasmic calcium.

Despite droperidol's structural similarity to haloperidol, when droperidol (10, 25, and 50 μM) was added directly to the muscle bath, succinylcholine-induced contractures were less than control values. In addition, droperidol did not enhance succinylcholine-induced contractures when the muscle was further challenged by the addition of halothane. When 100 μM droperidol was added to the muscle bath, the protective effect appeared to be reduced. However, those doses of droperidol greater than 10 μM are several-fold higher than anesthetic plasma concentrations, which were reported to be as high as 2367 ng/mL (27) or equivalent to approximately 6 μM (14). Results of the present investigation support those from other in vitro studies (14,15) that suggest that droperidol may minimize as well as protect against skeletal muscle contracture.

Like haloperidol, trifluoperazine produced significant increases in contracture for all in vitro experimental conditions. However, unlike haloperidol when added alone in vitro, trifluoperazine did not induce skeletal muscle contracture. Trifluoperazine binds selectively to the calcium-dependent activator of cyclic nucleotide phosphodiesterase, calmodulin (28–31), and thus activates calcium adenosine triphosphatase (32). However, interaction with calmodulin may not be the sole mode of action of trifluoperazine. The amphiphilic properties of trifluoperazine may allow the drug to initiate subtle structural perturbations by partitioning in cellular membranes including those of the sarcoplasmic reticulum (33). Thus, the activity of membrane-bound enzymes such as calmodulin-independent adenosine triphosphatases or calcium pumps would be affected.

Interpretation of the results after pretreatment with haloperidol, droperidol, or trifluoperazine is complicated by the complex interactions that occur in vivo, which may include drug metabolites and catecholamine levels. Some neuroleptic agents, even after a single dose, may have prolonged activity or retention in tissue (34). The results of this study are those from a single dose administered over a short period of time rather than based on results of chronic treatment with neuroleptic agents. The lowest dose administered (0.35 mg/kg) in vivo most closely approximates the therapeutic dose for the neuroleptic agents, but is nonetheless several-fold higher than the normal clinical range. The rationale for choice of these in vivo pretreatment amounts was based on the results of a study in which haloperidol was used as a pretreatment 6–12 h before the administration of 2,4-dinitrophenol. A dose-dependent decrease in hyperpyrexia was observed when 0.35 and 0.70 mg/kg haloperidol was used (19).

In vivo pretreatment with droperidol significantly reduced contractures for all triggering conditions. These results together with those from in vitro studies support the contention that droperidol may be considered as a safe anesthetic adjunct for use with MH-susceptible patients. However, it is important to note that the ability of droperidol to moderate the contracture-inducing effects of halothane may preclude its use before diagnostic muscle testing.

Results of in vivo and in vitro experiments with both haloperidol and trifluoperazine present an interesting paradox. When these two drugs were added in vitro, significant increases in contracture values were observed. However, in vivo pretreatment with trifluoperazine produced significant decreases in tension for all triggering conditions, and pretreatment with haloperidol significantly reduced succinylcholine-induced contractures. With subsequent addition of halothane, significant potentiation of contractures was not observed. These results illustrate one of the inherent problems of interpreting results from in vitro studies. That is, not all effects or drug actions may be adequately reflected in the in vitro model even though it eliminates many of the complex interactive factors of the in vivo milieu. It is conceivable that in vitro drug interactions may not occur in the in vivo environment and vice versa.

The usefulness of an animal model when there is limited access to muscle from MH-susceptible humans or swine is unquestionable. However, the relationship of the contracture response of MH-susceptible muscle to the contracture response induced by succinylcholine and halothane in this study is unknown. Results from in vivo pretreatment with haloperidol and trifluoperazine have implications for those studies that employ in vitro muscle contracture tests to determine MH susceptibility in NMS survivors. Results of the present study demonstrate the ability of these neuroleptic agents to inhibit the contracture-inducing and exacerbating effects of succinylcholine and halothane. Therefore, caution should be used in interpreting results from studies that employ muscle biopsy specimens from NMS individuals who are not drug-free for a considerable period of time before contracture testing.

References

1. Gronert GA. Malignant hyperthermia. Anesthesiology 1980; 53:395–423.
2. Britt BA. Combined anesthetic- and stress-induced malignant hyperthermia in two offspring of malignant hyperthermic-susceptible parents. Anesth Analg 1988;67:393–9.
3. Delay J, Daniker P. Drug-induced extrapyramidal syndromes. In: Vinken PJ, Bruyn GW, eds. Handbook of clinical neurology. Volume 6. Diseases of basal ganglia. Amsterdam: North Holland Publishing, 1968:248–66.
4. Caroff SN. The neuroleptic malignant syndrome. J Clin Psychiatry 1980;41:79–83.
5. Weinberg S, Twersky RS. Neuroleptic malignant syndrome. Anesth Analg 1983;62:845–50.
6. Caroff SN, Rosenberg H, Fletcher JE, Heiman-Patterson TD, Mann SC. Malignant hyperthermia susceptibility in neuroleptic malignant syndrome. Anesthesiology 1987;67:20–5.
7. Lopez JR, Sanchez V, Lopez MJ. Sarcoplasmic ionic calcium concentrations in neuroleptic malignant syndrome. Cell Calcium 1989;10:223–33.
8. Kurlan R, Hamill R, Shoulson I. Neuroleptic malignant syndrome. Clin Neuropharmacol 1984;7:109–20.
9. Wingard DW. Proceedings of the Focus Malignant Hyperthermia Symposium, Wausau, Wisconsin, September 13, 1974. New York: Appleton-Century-Crofts, 1977.
10. Wingard DW, Gatz EE. Some observations on stress susceptible patients. In: Aldrete JA, Britt BA, eds. Malignant hyperthermia. New York: Grune & Stratton, 1978:363–72.
11. McGrath CJ, Rempel WE, Jessen CR, et al. Protection from halothane-induced porcine hyperthermia syndrome by droperidol. Lab Anim Sci 1980;30:992–6.
12. McGrath CJ, Rempel WE, Addis PB, et al. Acepromazine and droperidol inhibition of halothane induced malignant hyperthermia (porcine stress syndrome) in swine. Am J Vet Res 1981;42:195–8.
13. Collins SP, White MD, Denborough MA. Calmodulin-antagonist drugs and porcine malignant hyperpyrexia. Clin Exp Pharmacol Physiol 1988;15:473–7.
14. Fletcher JE, Rosenberg H, Lizzo F. Effects of droperidol, haloperidol and ketamine on halothane, succinylcholine and caffeine contractures: implications for malignant hyperthermia. Acta Anaesthesiol Scand 1989;33:1–6.
15. Fletcher JE, Rosenberg H, Hilf M. In vitro studies of droperidol for use in human malignant hyperthermia. Anesthesiology 1985;63:A302.
16. Raess BU, Vincenzi FF. Calmodulin activation of red blood cell ($Ca^{2+} + Mg^{2+}$)-ATPase and its antagonism by phenothiazines. Molec Pharmacol 1980;18:253–8.
17. Landers DF, Becker GL, Wong KC. Calcium, calmodulin, and anesthesiology. Anesth Analg 1989;69:966–78.
18. Fletcher JE, Rosenberg H. In vitro muscle contractures induced by halothane and suxamethonium. I. The rat diaphragm. Br J Anaesth 1986;58:1427–32.
19. Gatz EE, Jones JR. Haloperidol antagonism to the hyperpyrexia and lethal effects of 2,4-dinitrophenol in rats. Anesth Analg 1970;49:773–80.
20. Fletcher JE, Rosenberg H. In vitro interaction between halothane and succinylcholine in human skeletal muscle. Implications for malignant hyperthermia and masseter muscle rigidity. Anesthesiology 1985;63:190–4.
21. Harrison GG. Anesthetic-induced malignant hyperpyrexia. A suggested method of treatment. Br Med J 1971;3:454–6.
22. Moulds RFW, Denborough MA. Identification of susceptibility to malignant hyperpyrexia. Br Med J 1971;2:245–7.
23. Lucke JN, Hall GM, Lister D. Porcine malignant hyperthermia. I. Metabolic and physiological changes. Br J Anaesth 1976;48: 297–304.
24. Kalow W, Britt BA, Richter A. The caffeine test of isolated human muscle in relation to malignant hyperthermia. Can Anaesth Soc J 1977;24:678–94.
25. Halsall PJ, Ellis FR. A screening test for the malignant hyperpyrexia phenotype using suxamethonium-induced contracture of muscle treated with caffeine, and its inhibition by dantrolene. Br J Anaesth 1979;51:753–6.
26. Araki M, Takagi A, Higuchi I, Sugita H. Neuroleptic malignant syndrome: caffeine contracture of single muscle fibers and muscle pathology. Neurology 1988;38:297–301.
27. Fischler M, Bonnet F, Trang H, et al. The pharmacokinetics of droperidol in anesthetized patients. Anesthesiology 1986;64: 486–9.

28. Levin RM, Weiss B. Mechanism by which psychotropic drugs inhibit adenosine cyclic 3′,5′-monophosphate phosphodiesterase in brain. Molec Pharmacol 1976;12:581–9.

29. Levin RM, Weiss B. Binding of trifluoperazine to the calcium-dependent activator of cyclic nucleotide phosphodiesterase. Molec Pharmacol 1977;13:690–7.

30. Cheung WY. Calmodulin plays a pivotal role in cellular regulation. Science 1980;207:19–27.

31. Conner CG, Levin R, Brownstein BL. The effects of trifluoperazine on calcium uptake and calcium-dependent functions in cultured epithelial cells. Biol Cell 1982;46:37–42.

32. Levin RM, Weiss B. Specificity of the binding of trifluoperazine to the calcium-dependent activator of phosphodiesterase and to a series of other calcium binding proteins. Biochim Biophys Acta 1978;540:197–204.

33. Ho MM, Scales DJ, Inesi G. The effect of trifluoperazine on the sarcoplasmic reticulum membrane. Biochim Biophys Acta 1983;730:64–70.

34. Campbell A, Baldessarini RJ, Teicher MH, Kula NS. Prolonged antidopaminergic actions of single doses of butyrophenones in the rat. Psychopharmacology 1985;87:161–6.

Clinical Responses to ORG 9426 During Isoflurane Anesthesia

Timothy J. Quill, MD, Maurice Begin, CRNA, Peter S.A. Glass, MD, Brian Ginsberg, MD, and Michael S. Gorback, MD

QUILL TJ, BEGIN M, GLASS PSA, GINSBERG B, GORBACK MS. Clinical responses to ORG 9426 during isoflurane anesthesia. Anesth Analg 1991;72:203–6.

To determine average dose requirements and pharmacodynamic characteristics before general clinical use, the dose-response curve, onset time, and recovery time for the neuromuscular relaxant ORG 9426 were determined in 72 adult patients given doses of 120, 160, 200, or 240 μg/kg after establishment of a steady-state expired isoflurane concentration of approximately 1%. Neuromuscular blockade was continuously recorded using the ulnar evoked electromyogram. Using the log probit method, ED_{95} was 268 μg/kg, ED_{90} was 251 μg/kg, and ED_{50} was 144 μg/kg. The time until 80% blockade was 1.9 min at 240μg/kg, and the average time to peak effect was 4.6 min, which did not vary with dose. The clinical duration (injection until T1 returned to 25%) was 20.5 min, and the recovery index (T1 increased from 25% to 75% of control) was 15.4 min, after a total dose of 300 μg/kg. The duration of 75-μg/kg and 100-μg/kg repeat (maintenance) dose was 14.6 and 17.8 min, respectively, and no cumulative effect was apparent after as many as five maintenance doses. No cardiovascular side effects were seen at doses used in the study. We conclude that ORG 9426 is a nondepolarizing muscle relaxant with a rapid onset and short duration of action that deserves further clinical evaluation.

Key Words: ANESTHETICS, VOLATILE—isoflurane. NEUROMUSCULAR RELAXANTS—ORG 9426.

ORG 9426 (the 2-morpholino, 3-hydroxy, 16*N*-allylpyrrolidino analogue of vecuronium) is a steroidal competitive muscle relaxant chemically similar to vecuronium. Animal studies (1–3) have reported ORG 9426 to be an effective muscle relaxant that is substantially less potent than vecuronium, but with a more rapid onset of action and with negligible cardiovascular and vagal side effects. Initial human evaluations (4–6) predicted an ED_{90} of 200–400 μg/kg under nitrous oxide-narcotic general anesthesia with a more rapid onset than seen with pipecuronium, with a short duration of action (6), and no cardiovascular or other side effects. The administration of ORG 9426 to patients during potent inhalation general anesthesia has not been previously reported. This study was conducted to evaluate further the pharmacology of ORG 9426 in patients and to determine, in particular, (a) the average human dose response of ORG 9426 in healthy adult human subjects during isoflurane anesthesia; (b) whether changes in blood pressure or heart rate are seen with injection of ORG 9426 doses at or below 240 μg/kg; (c) the average times of onset and duration of action; and (d) whether a cumulative effect occurs with repeated doses.

Methods

With institutional review board approval and after obtaining written informed consent, 72 adult subjects scheduled for elective surgery were randomized into one of four groups scheduled to receive either 120, 160, 200, or 240 μg/kg of ORG 9426. All patients were ASA physical status I or II and were free of hepatic, renal, or neuromuscular disease and extreme obesity. Neuromuscular blockade was evaluated using a Puritan-Bennett model ABM-100 evoked electromyograph (EMG) unit stimulating the ulnar nerve at the wrist with surface electrodes every 20 s and measuring the response of the hypothenar muscles. Blood pressure and heart rate were measured every 3 min using a Dinamap model 1846 SX noninvasive blood pressure monitor via a brachial cuff. Electromyograph and cardiovascular monitors were connected via serial data link to an "IBM/AT-compatible" microcomputer running custom interactive data acquisition software recording automatically every 20 s. Inspired

---

Supported in part by a grant from Organon, Inc.
Received from the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina. Accepted for publication September 28, 1990.

Address correspondence to Dr. Quill, Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

and expired carbon dioxide, nitrous oxide, and isoflurane were continuously measured using an Albion RASCAL anesthetic gas monitor.

Patients were premedicated with 5–10 mg oral diazepam. On arrival in the operating room, automatic data acquisition was initiated and general anesthesia was induced using 4–7 mg/kg thiopental and 1–3 μg/kg fentanyl. Isoflurane at 5% inspired concentration and nitrous oxide at 50% inspired concentration were started after induction as soon as a clear airway was assured. As soon as an adequate depth of anesthesia was achieved, tracheal intubation was accomplished without the use of neuromuscular relaxants. After tracheal intubation, inspired isoflurane concentration was adjusted to obtain a stable end-expiratory concentration of 1.0%.

On reaching a stable end-expiratory concentration of isoflurane, the EMG evoked response was calibrated to 100% reference and the patient was given a randomized dose of ORG 9426 by rapid bolus administration through a freely flowing peripheral intravenous catheter. After EMG suppression following the first dose reached a maximum, determined by three successive unchanged readings of T1 (of the train-of-four), a second dose was administered, calculated to give every subject a total (initial + second) dose of 300 μg/kg. Thereafter, doses of either 75 or 100 μg/kg of ORG 9426 were administered whenever T1 returned spontaneously to 25% of baseline level. Near the completion of surgery, spontaneous full recovery was allowed when possible, but patients in whom either T1 or T4/T1 (ratio of the fourth to first response) failed to recover spontaneously to 75% were pharmacologically reversed with 40 μg/kg neostigmine preceded by 15 μg/kg atropine. Patients were extubated following completion of the surgical procedure, after adequate neuromuscular function had been restored as determined by sustained head-lift.

Data from the automated computer records were analyzed at the conclusion of the study. All EMG data were expressed as T1 (percent of control) of the train-of-four, with the maximum suppression (lowest T1) at the selected dose as well as the time between injection and the maximum suppression recorded for each patient and averaged for each of the doses. The times between injection of the second dose until recovery to 25% (clinical duration), 10%–25%, 25%–50%, and 25%–75% of EMG T1 baseline (when available) were measured and pooled for all patients. The duration of action of repeated doses was measured separately for the 75- and 100-μg/kg doses and for the first to the fifth repeat dose as the average time between injection and recovery of the EMG to 25% of baseline.

Table 1. ORG 9426 Dose Response and Onset Times

Dose (μg/kg)	Peak effect (T1 %)	Onset (min)[a]
120	61.3 ± 19.7	4.3 ± 1.7
160	44.8 ± 19	4.8 ± 1.2
200	28.7 ± 14.9	4.5 ± 1.3
240	10.0 ± 6.9	4.6 ± 1.4

[a] Time from injection until T1 reached the minimum value.

Blood pressure and heart rate data just before initial ORG 9426 injection and 3 min later were analyzed for possible associated hemodynamic changes.

One-way analysis of variance was used to evaluate the significance of variation in dose response and hemodynamic changes between the four dosage groups. ED_{50}, ED_{90}, and ED_{95} were calculated by the logarithmic least-squares regression equation of the resulting single-dose response data (7). Blood pressure and heart rate differences were analyzed by paired *t*-testing of the preinjection and 3-min postinjection values for each patient in each of the four dosage groups. All results were rounded to the nearest tenth and are expressed as mean ± SD. Differences were considered statistically significant at $P < 0.05$.

Results

Seventy-two patients were studied: 52 women and 20 men. Their average age was 43.6 ± 13.4 yr and average weight was 74 ± 15 kg. The evoked EMG data from one patient were unreadable, because of electrocautery interference, and another patient had only a minimal response to even 300 μg/kg of ORG 9426, and was rejected as the only outlier (>3 × SD). Thus, the evoked EMG data from 70 patients were analyzed. Hemodynamic data from two patients were excluded from analysis. One of these required ephedrine for treatment of hypotension associated with induction (before ORG 9426 administration), and in a second patient tracheal intubation was, for clinical reasons, done during hemodynamic data collection. Thus, hemodynamic data from 70 of the 72 patients were analyzed.

The dose-response results (Table 1 and Figure 1) show an expected increasing effect with increasing dose (analysis of variance, $P < 0.01$). ED_{50}, ED_{90}, and ED_{95}, calculated by logarithmic regression of the dose-response data, are 144, 251, and 268 μg/kg, respectively. The time from injection until T1 decreased to 20% of baseline in the 240-μg/kg group was

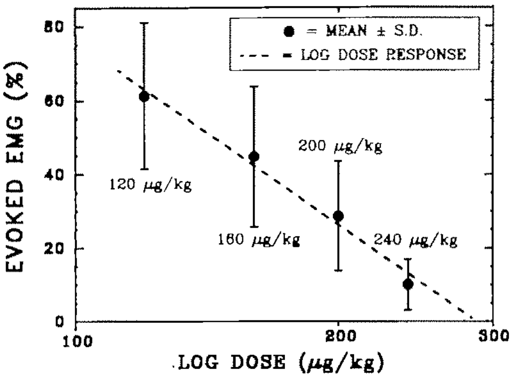


Figure 1. Minimum evoked EMG (T1 of train-of-four—%) ± SD versus dose for ORG 9426 during isoflurane general anesthesia in humans. Regression equation shown as *dashed line*: $y = 408.8 - 72.2 \cdot \ln(x)$.

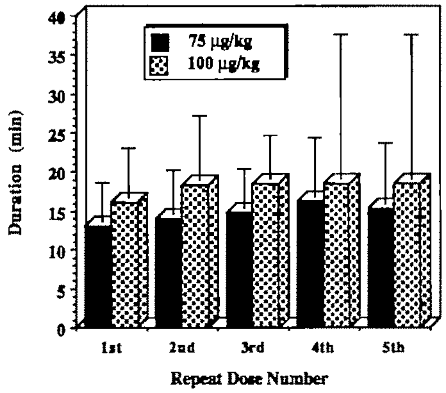


Figure 2. Duration (time between injection until return of T1 to 25% of baseline) versus number of repeat doses. No significant difference was observed as a function of number of doses, but in the 75-μg/kg group duration was significantly less than in the 100-μg/kg group.

1.9 ± 1.0 min (lower doses did not consistently result in 20% T1), and the time until T1 reached the minimum value was 4.6 ± 1.2 min, with no difference between dosage groups (Table 1). The time for recovery of EMG response to 25% of baseline (measured from when the 300-μg/kg total dose was administered) averaged 20.5 ± 8.8 min. Time from 10% to 25% recovery averaged 8.0 ± 2.5 min ($n = 39$), from 25%–50% recovery 7.5 ± 2.8 min ($n = 15$), and from 25%–75% recovery 15.4 ± 8.9 min ($n = 11$). The duration of action of repeat doses, calculated as the time from injection until recovery to 25%, is shown in Figure 2 for one to five injections of either 75 or 100 μg/kg.

A difference was observed between the average duration of 75- and 100-μg/kg doses (14.6 ± 6.0 min and 17.8 ± 6.3 min, respectively), but there was no significant difference in duration of action related to the number of repeat doses (Figure 2).

Pooled average mean blood pressure data from all dose groups decreased from 81.3 ± 16.4 mm Hg to 75.0 ± 13.3 mm Hg, and heart rate decreased from 81.4 ± 19.5 beats/min to 76.1 ± 15.2 beats/min, measured in both instances from just before and 3 min after the first dose of ORG 9426. In the individual analyses for the two highest dose groups (200 and 240 μg/kg), however, there were no dose-dependent changes in either heart rate or blood pressure.

Discussion

This study investigated the human dose response of ORG 9426, a new nondepolarizing neuromuscular blocker, during isoflurane general anesthesia. Animal and existing human studies (1–6,8) suggest that ORG 9426 is potentially a useful and safe nondepolarizing muscle relaxant with a significantly more rapid onset of action than currently available nondepolarizing agents, with a potency approximately one-fifth that of vecuronium. The dose-response data observed in this study (ED_{50} = 144 μg/kg, ED_{95} = 268 μg/kg) agree well with reported results for nitrous-narcotic anesthesia (9) (ED_{50} = 168 μg/kg, ED_{95} = 285 μg/kg), with the difference attributed to the effect of isoflurane.

We studied 72 patients without complication or apparent adverse effect. A single subject undergoing an orthopedic procedure had only a 22% maximum reduction of T1 after 300 μg/kg of ORG 9426, and her data were excluded from neuromuscular analysis. Clinical history and examination revealed no satisfactory explanation for her lack of response, except that she had been bedridden and inactive for several weeks as a result of long bone fractures. One patient required that the first ORG 9426 dose be administered to facilitate failed intubation despite a 20-min mask administration of isoflurane. Another patient was given 10 mg of ephedrine for moderate induction-related hypotension just before ORG 9426 administration. The data from these latter two patients were excluded from hemodynamic analysis because blood pressure and heart rate were significantly affected during the measurement period.

End-expired isoflurane concentration at the time of ORG 9426 administration was maintained as close to 1.0% as possible (0.9% ± 0.4%), but the achieved concentration had to be decreased in several patients to as low as 0.5% to maintain a normal blood pressure.

Very large doses of ORG 9426 (>1000 μg/kg) in animals produced a slight increase in heart rate and a slight decrease in blood pressure (2). Cardiovascular effects observed in this study consisted of a slight decrease in blood pressure and heart rate 3 min after injection of ORG 9426. Analysis of data from each individual dose group, however, revealed no statistical significance of changes in blood pressure or heart rate in the two higher dose groups, and a lack of a dose-dependent change in heart rate or blood pressure. Therefore, observed hemodynamic changes probably were related to the clinical state at the time of the first dose (i.e., surgical levels of anesthesia without surgical stimulation), and were not due to the relaxant itself. On this basis, we conclude that there were no clinically significant changes in blood pressure or heart rate at doses at or below 240 μg/kg as a result of ORG 9426 administration.

The rapid onset of neuromuscular blockade during anesthetic induction is desirable in many clinical situations. Succinylcholine demonstrates both a very rapid onset time and a rapid recovery, but is associated with several side effects particular to depolarizing neuromuscular blockers. The average onset time observed in this study, defined as the time from injection until maximum effect, was 4.6 ± 1.4 min and did not vary with dose (Table 1). This value is shorter than the 6–7 min reported for equally effective doses of vecuronium (10).

The time until T1 decreased to 20% of baseline, in patients given 240 μg/kg of ORG 9426, was 114.0 ± 58.0 s, similar to the results of others (6), and this value is also similar to that observed (133.5 ± 28.8 s) using much higher relative doses ($300 \mu g/kg \cong 6 \times ED_{90}$) of vecuronium (9). Thus, ORG 9426 may indeed have a more rapid onset of action than currently available nondepolarizing muscle relaxants without resulting in a prolonged duration of action (9), but further studies are indicated to confirm this.

The average time of recovery of EMG response to 25% of baseline values, measured at 20.5 ± 8.8 min after a total dose of 300 μg/kg, should be interpreted in light of the fact that each patient received two divided doses separated by approximately 4 min; therefore, the recovery time to 25% of a single bolus of 300 μg/kg may have been different (7).

In conclusion, our results confirm that ORG 9426 produces effective surgical relaxation and demonstrates a potency ($ED_{90} \cong 250$ μg/kg) in humans approximately one-fifth to one-seventh that of vecuronium ($ED_{90} \cong 50$ μg/kg) (7,10) during isoflurane general anesthesia. There appear to be no cardiovascular side effects at doses at or below 240 μg/kg. Recovery and onset were rapid and predictable, and no cumulative effects were seen. Further studies are desirable to evaluate the onset characteristics at higher doses, and to determine the average dose and efficacy of ORG 9426 continuous infusions.

References

1. Muir AW, Houston J, Green KL, Marshall RJ, Bowman WC, Marshall IG. Effects of a new neuromuscular blocking agent (ORG 9426) in anaesthetized cats and pigs and in isolated nerve-muscle preparations. Br J Anaesth 1989;63:400–10.
2. Investigator's Brochure, ORG 9426, December 1988 (Internal Document of Organon, Inc.).
3. Khuenl-Brady K, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S, Miller RD. The neuromuscular blocking effects and pharmacokinetics of ORG 9426 and ORG 9616 in the cat. Anesthesiology 1990;72:669–74.
4. Wierda JM, Dewit AP, Kuizenga K, Agoston S. Clinical observations on the neuromuscular blocking action of ORG 9426, a new steroidal non-depolarizing agent. Br J Anaesth 1990;64:521–3.
5. Nagashima H, Nguyen HD, Kinsey A, et al. The human dose response of ORG 9426. Anesthesiology 1989;71:A772.
6. Witkowski TA, Bartkowski RR, Azad SS, Epstein RH, Marr A, Lessin J. ORG 9426, a new short-acting muscle relaxant: onset and duration of action. Anesth Analg 1990;70:S437.
7. Gibson FM, Mirakhur RK, Clarke RS, Lavery GG. Comparison of cumulative and single bolus techniques for determining the potency of vecuronium. Br J Anaesth 1985;57:1060–2.
8. Foldes FF, Chadhry I, Goldiner PL, Nagashima H. The in-vitro neuromuscular effects of ORG 9426 in rodents. Anesthesiology 1989;71:A772.
9. Ginsberg B, Glass PSA, Quill TJ, Shaffron D, Ossey KD. Onset and duration of neuromuscular blockade following high dose vecuronium administration. Anesthesiology 1989;71:201–5.
10. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P. Clinical pharmacology of ORG NC45: a new non-depolarizing muscle relaxant. Anesthesiology 1981;55:6–11.

Cardiorespiratory Effects of Antagonism of Diazepam Sedation With Flumazenil in Patients With Cardiac Disease

Eran Geller, MD, Pinchas Halpern, MD, Joseph Chernilas, MD, David Niv, MD, and Hylton B. Miller, MB

GELLER E, HALPERN P, CHERNILAS J, NIV D, MILLER HB. Cardiorespiratory effects of antagonism of diazepam sedation with flumazenil in patients with cardiac disease. Anesth Analg 1991;72:207–11.

The specific benzodiazepine antagonist flumazenil is currently under intense study. Despite much clinical experience, no detailed invasive hemodynamic studies of its use in cardiac patients have been published. In the present study, hemodynamic and respiratory variables were measured in 10 cardiac patients undergoing catheterization of the right and left sides of the heart, before and after sedation with intravenous diazepam, and after reversal of sedation with flumazenil. A sleep dose of diazepam (12.2 ± 5.1 mg, mean ± SD) caused only slight decreases in mean arterial pressure (103 ± 12 to 98 ± 14 mm Hg; $P < 0.05$), pulmonary capillary wedge pressure (13.2 ± 6.3 to 11.7 ± 6.6 mm Hg; $P < 0.05$), and left ventricular end-diastolic pressure (20.8 ± 7.5 to 17.3 ± 10.0 mm Hg; $P < 0.05$), with no significant changes in respiratory gas homeostasis. Intravenous flumazenil (0.22 ± 0.07 mg) resulted in spontaneous awakening and return to full orientation, yet caused no significant alteration in either hemodynamic or respiratory variables measured. Reversal of diazepam-induced sedation by flumazenil in cardiac patients appears safe and effective.

Key Words: ANTAGONISTS, MISCELLANEOUS—benzodiazepines, flumazenil. HYPNOTICS, BENZODIAZEPINES—diazepam.

Benzodiazepines are among the most widely used drugs in clinical medicine. Because of their mild cardiovascular effects, they are frequently selected for sedation or anesthesia in patients suffering from myocardial dysfunction. However, the large variability in individual sensitivity to the central nervous system depressant effects of the benzodiazepines may sometimes result in respiratory depression, prolonged somnolence, or even coma. It is therefore desirable to have the capability of rapidly terminating at will the effects of benzodiazepines without having to wait for normal metabolic degradation and excretion to occur.

Recently, a specific benzodiazepine receptor antagonist, flumazenil, was approved for clinical investigation (1). Although extensive experience with flumazenil has already been acquired from studies in animals and human volunteers, few data exist regarding the cardiorespiratory effects of antagonizing the sedative action of diazepam in patients with heart disease. Certainly there are no reports of extensive invasive hemodynamic studies in patients with significant coronary artery or valvular disease. In the present study the hemodynamic effects of the administration of flumazenil after diazepam-induced sleep were evaluated in 10 patients undergoing cardiac catheterization.

Methods

Ten patients undergoing cardiac catheterization and coronary angiography for evaluation of moderate to severe coronary artery disease (seven patients) or valvular lesions (three patients) comprised the study group. Patient characteristics as well as data before and after catheterization are listed in Table 1. Institutional approval and informed written consent were obtained before the study.

Patients were premedicated orally with 10 mg diazepam approximately 1 h before arrival in the catheterization laboratory. A peripheral venous cath-

---

Received from the Department of Anesthesiology, and Intensive Care Unit, and the Department of Cardiology, Tel Aviv Medical Center, Ichilov Hospital, and the Tel Aviv University Sackler Faculty of Medicine, Tel Aviv, Israel. Accepted for publication October 3, 1990.

Address correspondence to Dr. Geller, Department of Anesthesiology and ICU, Ichilov Hospital, 6 Weitzman Street, Tel Aviv 64239, Israel.

©1991 by the International Anesthesia Research Society

Table 1. Characteristics of the Patient Group

Patient	Sex	Age (yr)	Diagnosis before catheterization	Medications before catheterization	Diagnosis after catheterization
1	M	65	AST, alcoholism	—	Moderate AST
2	F	60	AST	—	Severe AST, 1 vessel CAD
3	M	65	MS, CHF	Furosemide, digoxin	MS
4	M	48	Stable AS, MI (twice)	Propranolol, isosorb	2 vessel CAD
5	M	64	Stable AS, PVD	Atenolol, isosorb	3 vessel CAD
6	F	69	Stable AS, DM	Nifedipine, atenolol	3 vessel CAD
7	M	58	Stable AS, DM	Verapamil, isosorb	3 vessel CAD
8	M	61	Stable AS	Isosorb	3 vessel CAD
9	M	65	Unstable AS	Verapamil	3 vessel CAD
10	M	64	Unstable AS	Nifedipine	3 vessel CAD

AST, aortic stenosis; CAD, coronary artery disease; MS, mitral stenosis; CHF, congestive heart failure; AS, anginal syndrome; MI, myocardial infarction; PVD, peripheral vascular disease; DM, diabetes mellitus.

eter was inserted for the slow infusion of 5% dextrose in water. Oxygen was continuously administered via a Venturi type mask delivering 40% oxygen at total flows of up to 50 L/min. After local infiltration with 2% lidocaine, a 7F balloon flotation catheter was inserted percutaneously via the right femoral vein and its tip was located in the main pulmonary artery. A 7F pig-tailed catheter was inserted into the left ventricle via the right femoral artery. Both catheters were connected to Statham P23ID pressure transducers, a VR-12 E for M electronic monitor, and a Honeywell optical strip-chart recorder. With the patient supine the following variables were measured and recorded during the study: heart rate, right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, mean systemic arterial pressure, and left ventricular end-diastolic pressure. All pressures were recorded at end-expiration. Thermodilution cardiac output was measured in triplicate, using 10-mL boluses of ice-cold 5% dextrose in water, with an Edwards Laboratories 9520 cardiac output computer. Cardiac index and systemic and pulmonary vascular resistances were calculated using standard formulas. Arterial and mixed venous blood samples were drawn simultaneously and immediately analyzed for Po_2, Pco_2, and pH using an AVL 945 blood gas analyzer. The following variables were calculated: arterial and venous oxygen contents, arteriovenous oxygen content difference, oxygen delivery (i.e., arterial O_2 content times cardiac output), oxygen consumption by the inverse Fick method, and arterial Po_2 to fraction inspired oxygen tension ratio.

Patients were allowed to stabilize for 15 min after insertion of the catheters before baseline measurements were obtained. All patients were calm and hemodynamically stable. Diazepam was then injected intravenously at a rate of 5 mg/min until patients were unresponsive to verbal stimulation (mean total dose 12.2 ± 5.1 mg). Five minutes later all measurements were repeated. Next, flumazenil was administered intravenously in 0.1-mg increments every 30 s until all patients became spontaneously awake and responsive to verbal commands with full orientation as to self, time, and place (mean dose, 0.22 ± 0.07 mg). Five minutes later all measurements were repeated. Patients were allowed to rest supine during the observation periods. The remainder of the catheterization procedure was then completed while patients were observed for signs of resedation or discomfort.

Statistical analysis of the data was performed using repeated measures analysis of variance. $P < 0.05$ was considered statistically significant.

Results

Measured and calculated hemodynamic variables are summarized in Table 2. A slight but statistically significant decrease in mean systemic arterial pressure, pulmonary capillary wedge pressure, and left ventricular end-diastolic pressure is evident after sedation with diazepam. All other variables remained unchanged. Flumazenil administration resulted in no significant change in either measured or calculated variables. When compared with prediazepam values, only left ventricular end-diastolic pressure remained slightly but significantly decreased. Respiratory gas homeostasis remained unchanged after both diazepam and flumazenil (Figure 1). All patients remained calm, cooperative, and awake for the remainder of the procedure, not requiring any further sedation. No local or systemic side effects attributable to flumazenil

Table 2. Hemodynamic Effects of Intravenous Diazepam and Flumazenil

Variable	Baseline	Diazepam (12.2 ± 5.1 mg)	Flumazenil (0.22 ± 0.07 mg)
HR (beats/min)	66 ± 17	67 ± 14	66 ± 15
MAP (mm Hg)	103 ± 12	98 ± 14[a]	101 ± 9
RAP (mm Hg)	6.3 ± 2.0	6.2 ± 1.4	6.4 ± 1.6
MPAP (mm Hg)	18.6 ± 6.5	17.5 ± 6.8	18.2 ± 6.5
PCWP (mm Hg)	13.2 ± 6.3	11.7 ± 6.6[a]	12.4 ± 6.4
LVEDP (mm Hg)	20.8 ± 7.5	17.3 ± 10.0[a]	17.6 ± 7.7[b]
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.7 ± 0.4	2.6 ± 0.5	2.6 ± 0.6
SVR ($dyne \cdot s^{-1} \cdot cm^{-5}$)	1584 ± 248	1571 ± 303	1628 ± 310
PVR ($dyne \cdot s^{-1} \cdot cm^{-5}$)	89 ± 17	99 ± 29	97 ± 26

HR, heart rate; MAP, mean systemic arterial pressure; RAP, right atrial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; CI, cardiac index; SVR, systemic vascular resistance; PVR, peripheral vascular resistance.

[a] $P < 0.05$ versus baseline.

[b] $P < 0.01$ versus baseline.

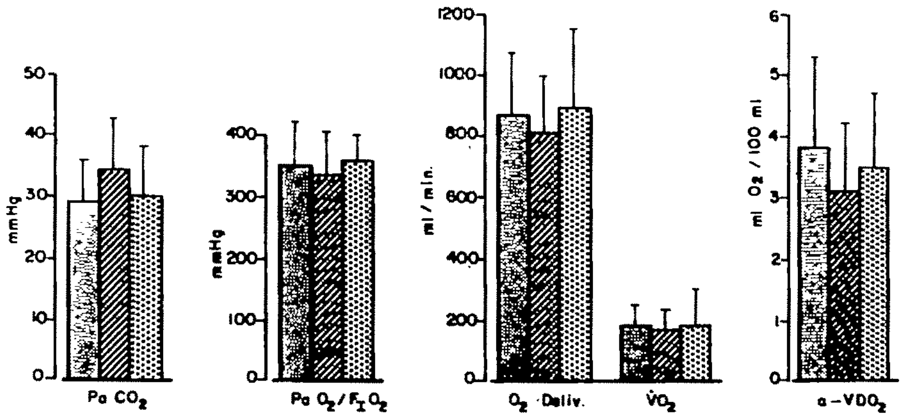


Figure 1. Respiratory gas data after a sleeping dose (12.2 ± 5.1 mg) of diazepam and after an awakening dose (0.22 ± 0.07 mg) of the specific benzodiazepine antagonist flumazenil in 10 patients with moderate to severe heart disease undergoing cardiac catheterization. *Bar with fine dots*, control; *bar with hatching*, after intravenous diazepam; *bar with large dots*, after intravenous flumazenil.

were observed, allowing the remainder of the procedure to be completed without incident in all cases. No evidence of resedation was noted during the 2-h observation period after the study.

Discussion

Flumazenil is a specific benzodiazepine antagonist that effectively antagonizes the characteristic centrally mediated effects of benzodiazepines by competing with these drugs at the central benzodiazepine receptor binding sites (1,2). In the present study the antagonization of diazepam-induced sleep was very rapid and complete (within 1–2 min), the patients remaining awake for the full 2-h observation period. These findings are in agreement with previous observations that the clinical effects of intravenous flumazenil become evident within as little as 28 s (3) and nearly always within 1–2 min (4), peak plasma concentrations being attained within less than 5 min (5). Penetration into the brain is very rapid, as shown by positron emission tomography (6), and elimination half-life is approximately 1 h (7). To avoid anxiety, a side effect sometimes noted with rapid administration of high doses of flumazenil (8), the drug should be titrated to desired effect, with small incremental doses (0.1–0.2 mg IV) being administered every 30–60 s until the desired response is achieved (7). By employing this approach, we were able to achieve satisfactory antagonization of sedation with only small doses of flumazenil (0.22 ± 0.07 mg) and with no untoward effects.

Flumazenil may possess mild intrinsic activity that is both agonistic and inverse agonistic in nature depending on the dose and on experimental conditions. Thus it has been shown that flumazenil has minor anticonvulsant effects (9); it reverses slow-wave sleep, possibly increases vigilance, and causes mild anxiety (7). Flumazenil has also been shown to facilitate recovery from halothane anesthesia in mice (10) and in humans (11).

The lack of hemodynamic excitation observed in this study was somewhat surprising in view of the rather abrupt awakening from diazepam-induced hypnosis. The present paper is, to our knowledge, the first published full, detailed, invasive hemodynamic study in patients with significant cardiac disease. The findings reported here are in agreement with a number of clinical studies of flumazenil in the postoperative period (8), in cardiac patients (12), and in critically ill patients in an intensive care unit (13). Marty et al. (12) reported on a study of 11 patients undergoing cardiac catheterization under flunitrazepam sedation. Antagonization of sedation with flumazenil was characterized by stable left ventricular function and coronary circulation during the 5–15-min observation period after flumazenil injection. Louis et al. (8), in another preliminary double-blind study of patients after open-heart surgery, found that antagonization of benzodiazepine sedation with a very high dose of flumazenil (0.1 mg/kg) caused psychological discomfort and even anxiety in some of the subjects, yet did not produce any significant cardiovascular effects during a 10-min observation period. Three milligrams of flumazenil administered intravenously and preoperatively to cardiac patients who had not previously received an agonist did not result in any significant hemodynamic effect (14).

These findings are also in agreement with our previous studies, in which flumazenil was used to antagonize the sedative effects of diazepam and midazolam administered for brief diagnostic and therapeutic procedures (15), for supplementation of regional anesthesia (16), for reversal of continuous midazolam sedation in the intensive care unit (13), in an unselected general hospital population, as well as for the treatment of intentional and iatrogenic overdoses (17). In none of these studies were any clinically significant untoward hemodynamic effects noted. However, no highly detailed, sophisticated, and invasive data in a group of patients with significant coronary artery or valvular disease have been reported to date. In the present study, in which detailed invasive hemodynamic measurements were made in a group of patients with heart disease, no clinically significant changes were observed after flumazenil injection.

The lack of hemodynamic response to antagonization of benzodiazepine-induced sedation with flumazenil may be related to the fact that no significant increases in levels of plasma catecholamines (18,19), glucose, cortisol (18), vasopressin, or β-endorphins (20) have been observed. Flumazenil does cause a rapid return to baseline of the benzodiazepine-induced decrease in plasma norepinephrine levels, both in healthy volunteers (21) and in surgical patients (22).

The principal effect of diazepam on respiratory gas homeostasis is mild and variable depression of ventilation occurring quickly and reaching a plateau 3–5 min after intravenous administration (23). In the present study respiratory variables remained relatively unchanged after diazepam administration. The slight increase in arterial P_{CO_2} that was noted was reversed by flumazenil, suggesting possible antagonization of the respiratory effects of diazepam.

In conclusion, the present study indicates that flumazenil effectively antagonizes diazepam-induced sedation and that its use in patients with moderate to severe cardiac disease is probably safe, being associated with minimal cardiovascular and ventilatory changes.

References

1. Hunkeler W, Mohler H, Pieri L, et al. Selective antagonists of benzodiazepines. Nature 1981;290:514–6.
2. Darragh A, Lambe T, Scully M, Brick I, O'Boyle C, Downie WW. Investigation in man of the efficacy of a benzodiazepine antagonist, Ro 15-1788. Lancet 1981;ii:8–10.
3. Lauven PM, Schwilden H, Stoeckel H, Greenblatt DJ. The effects of a benzodiazepine antagonist RO 15-1788 in the presence of stable concentrations of midazolam. Anesthesiology 1985;63:61–4.
4. Doenicke A. Modern trends in the investigation of new hypnotics in anaesthesia. In: Hinmarch I, Oh H, Roth T, eds. Sleep, benzodiazepines and performance. Berlin: Springer Verlag, 1984:119–32.
5. Klotz U, Ziegler G, Reinmann IW. Pharmacokinetics of the selective benzodiazepine antagonist RO 15-1788 in man. Eur J Clin Pharmacol 1984;27:115–7.
6. Samson Y, Hantraye P, Baron JC, et al. Kinetics and displacement of $[^{11}C]$Ro 15-1788, a benzodiazepine antagonist, studied in human brain in vivo by positron tomography. Eur J Pharmacol 1985;110:247–51.
7. Klotz U, Kanto J. Pharmacokinetics and clinical use of flumazenil (Ro 15-1788). Clin Pharmacokinet 1988;14:1–12.
8. Louis M, Forster A, Suter PM, Gemperle M. Clinical and hemodynamic effects of a specific benzodiazepine antagonist (RO 15-1788) after open heart surgery. Anesthesiology 1984; 61:A61.
9. Scollo-Lavizzari G. The anticonvulsant effect of the benzodiazepine antagonist RO 15-1788: an EEG study in 4 cases. Eur J Neurol 1984;23:1–6.
10. Geller E, Schiff B, Halpern P, Speiser Z, Cohen S. A benzodiazepine receptor antagonist improves emergence of mice from halothane anaesthesia. Neuropharmacology 1989;28:271–4.
11. Geller E, Weinbrum A, Schiff B, et al. The effects of flumazenil on the process of recovery from halothane anaesthesia. Eur J Anaesth 1988;2(Suppl):151–3.
12. Marty J, Nitenberg A, Philip I, et al. Myocardial metabolism and hemodynamics of midazolam in patients with coronary artery disease. Anesthesiology 1988;69:A110.
13. Geller E, Halpern P, Barzelai E, et al. Midazolam infusion and the benzodiazepine antagonist flumazenil for sedation of intensive care patients. Resuscitation 1988;16:S31–9.
14. Croughwell ND, Reves JG, Will CJ, Kasson BJ, Hawkins E. Safety of flumazenil in patients with ischaemic heart disease. Eur J Anaesth 1988;2(Suppl):177–82.

15. Geller E, Silbiger A, Niv D, Nevo Y, Belhassen D. The reversal of benzodiazepine sedation with RO 15-1788 in brief procedures. Anesthesiology 1986;65:A357.

16. Geller E, Niv D, Matzkin C, et al. The antagonism of midazolam sedation in 50 postoperative patients. Anesthesiology 1985;64:A28.

17. Geller E, Niv D, Weinbrum A, Halpern P, Sorkine P. The use of flumazenil in the treatment of 34 intoxicated patients. Resuscitation 1988;16(Suppl):57–62.

18. Nilsson A, Persson MP, Hartvig P, Wide L. Effect of total intravenous anaesthesia with midazolam/alfentanil on the adrenocortical and hyperglycaemic response to abdominal surgery. Acta Anaesthesiol Scand 1988;32:379–82.

19. Ritter JW, Flacke WE, Norel E, Gion H, Chen R, Hoshizaki G. Adrenergic and hemodynamic response to flumazenil (Ro 15-1788) reversal of midazolam sedation. Anesthesiology 1988; 69:A109.

20. White PF, Shafer A, Boyle WA, Doze VA. Stress response following reversal of benzodiazepine induced sedation. Eur J Anaesth 1988;2(Suppl):173–6.

21. Duka T, Ackenheil M, Noderer J, Doenicke A, Dorow R. Changes in noradrenaline plasma levels and behavioral responses induced by benzodiazepine agonist with the benzodiazepine antagonist Ro 15-1788. Psychopharmacology 1986;90: 351–7.

22. Marty J, Joyon D. Haemodynamic responses following reversal of benzodiazepine-induced anaesthesia or sedation with flumazenil. Eur J Anaesth 1988;2(Suppl):167–71.

23. Gross JB, Smith L, Smith TC. Time course of ventilatory response to carbon dioxide after intravenous diazepam. Anesthesiology 1982;57:18–21.

Comparison of Percutaneous Losses of Sevoflurane and Isoflurane in Humans

Stephen H. Lockhart, PhD, MD, Nobuhiko Yasuda, MD, Natalie Peterson, BS, Michael Laster, DVM, Shahram Taheri, BS, Richard B. Weiskopf, MD, and Edmond I. Eger II, MD

LOCKHART SH, YASUDA N, PETERSON N, LASTER M, TAHERI S, WEISKOPF RB, EGER EI II. Comparison of percutaneous losses of sevoflurane and isoflurane in humans. Anesth Analg 1991;72:212–5.

We studied the percutaneous losses of sevoflurane and isoflurane during administration and elimination in seven healthy male volunteers. Anesthesia was induced and maintained with fentanyl, midazolam, and/or thiopental, and nitrous oxide for 30 min, after which 1% sevoflurane and 0.4% isoflurane in 65% nitrous oxide were administered for 30 min. Inspired, end-tidal, and mixed-expired gas samples were collected during administration and for 5–7 days of elimination. To measure percutaneous loss, each subject's arm was enclosed in a glass cylinder sealed at both ends and with two ports, one for flushing with nitrogen and one for obtaining gas samples during the 30 min of administration and the first 150 min of elimination. Anesthetic concentrations in all samples were determined using gas chromatography. The surface area of the arm was measured and the total surface area was calculated. During administration and elimination, percutaneous loss of isoflurane was significantly greater than that of sevoflurane ($P < 0.05$). For both volatile agents, losses during elimination were greater than during administration ($P < 0.05$), but even when combined, these losses were too small to affect kinetic or metabolic studies based on mass balance.

Key Words: ANESTHETICS, VOLATILE—I-653, desflurane, isoflurane, halothane, sevoflurane.

Previous studies of the percutaneous loss of volatile halogenated anesthetics have provided two conclusions. First, the loss is small relative to total uptake (1), even if losses during anesthetic elimination are considered (2). Second, the rate of loss is proportional to anesthetic solubility (1,2). In one comparative study, the order of losses was desflurane (formerly I-653, a methyl-ethyl ether), followed by isoflurane (also a methyl-ethyl ether), then halothane (an alkane) (2).

The structure of sevoflurane, being a methyl-isopropyl ether, differs from desflurane, isoflurane, and halothane. To assess whether this difference would affect the proportional relationship between solubility and percutaneous loss, we concurrently measured percutaneous loss of sevoflurane relative to that of isoflurane during anesthetic administration and elimination. Isoflurane provided a control permitting comparison of these results with those from previous studies.

Methods and Materials

With approval from the University of California, San Francisco Committee on Human Research and informed consent of each subject, we studied seven healthy male (ASA I) volunteers (age, 23 ± 3 yr; weight, 72 ± 9 kg; height, 182 ± 8 cm [mean ± SD]).

After confirming that each subject had fasted for at least 8 h, anesthesia was induced and maintained by intravenous administration of midazolam, fentanyl, and/or thiopental. Vecuronium, 10 mg IV, was administered to facilitate tracheal intubation. Ventilation was controlled and adjusted to maintain end-tidal carbon dioxide between 35 and 45 mm Hg (measured by mass spectrometry). Blood pressure was measured by oscillotonometry (Dinamap). In

---

Supported in part by the Maruishi Clinical Research Program, the Anesthesia Research Foundation, and the University of California President's Fellowship.

Received from the Department of Anesthesia and the Cardiovascular Research Institute, University of California, San Francisco, California; and Jikei University, Tokyo, Japan. Accepted for publication October 6, 1990.

Address correspondence to Dr. Lockhart, Department of Anesthesia, Room S-455, Box 0464, University of California, San Francisco, CA 94143-0464.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

addition, we continuously monitored oxygen saturation (Nellcor N-200) and temperature using a thermocouple (Mon-a-therm) enclosed in an esophageal stethoscope.

After induction of anesthesia, we administered 70% nitrous oxide (N_2O) for 30 min, followed by 1% sevoflurane and 0.4% isoflurane, in 65% N_2O/35% oxygen for 30 min. Sevoflurane and isoflurane were delivered from premixed tanks calibrated against primary standards. Administration of the volatile agents was discontinued after 30 min, and anesthesia was maintained for 150 min thereafter with 65% N_2O and the intravenous agents previously mentioned. Each subject was allowed to awaken 150 min after administration of the volatile agents was discontinued.

During the first 30 min of N_2O administration, the right arm of each subject was enclosed in a glass cylinder 50 cm long and 12.5 cm in internal diameter. The distal end of the cylinder was sealed with glass; the proximal end was sealed to the subject's arm with Mylar film covered with 3M Steri-Drape to provide an airtight seal between the glass cylinder and the arm. The absence of a leak in the system was confirmed by pressurizing the cylinder with 100% nitrogen. The cylinder had two ports, one used for sampling and the other for flushing with nitrogen (8 L/min for 2 min) before administering and discontinuing the volatile agents, and every 15 min thereafter for the first 150 min of their elimination.

Samples (40 mL each) were drawn from the cylinder into 50-mL glass syringes before administration of the volatile agents, and at 10, 15, 20, 25, and 28 min during their administration. During the first 150 min of elimination, gas samples were collected at 15-min intervals with a flush (2-min) separating each interval. Within each interval, samples were obtained at 0 min, 6–7 min, and 13 min. Barbotage assured adequate mixing of gases before obtaining a sample. The cylinder was removed after the first 150 min of elimination and before tracheal extubation.

We collected and analyzed end-tidal (FA), mixed-expired (FM), and inspired (FI) gas samples during the 30-min administration period, the first 150 min of elimination, and daily for the ensuing 5–7 days. We measured ventilation (VE) by spirometry.

Gas samples were analyzed for anesthetic concentration using a Gow-Mac Series 580 chromatograph with a column composed of 10% SF 96 on Chromasorb WHP, 68/80-mesh, maintained at 48°C. A nitrogen carrier stream flowing at 6 mL/min was delivered through the column to a flame ionization detector at 150°C, supplied by hydrogen at 10 mL/min and by air at 200 mL/min. Calibration (tank) standards were injected at intervals during the analysis. Peak height was proportional to concentration over the range of concentrations studied.

We calculated total percutaneous loss (PL) of the volatile anesthetics during each interval from the relationship

$$PL = V \cdot (TSA/ASA) \cdot \Delta,$$

where V is the volume of gas surrounding the arm in the glass cylinder (mL), TSA is the total body surface area (m^2), ASA is the arm surface area (m^2), and Δ is the difference between the anesthetic concentrations measured at the end and at the beginning of the interval (vol%/100). The volume was measured by displacement. The total body surface area was calculated from height and weight (3), and the arm surface area was measured by wrapping the arm with a single layer of aluminum foil. Weight of the foil per square centimeter was determined independently.

Within each 15-min interval, samples taken at 6–7 min and at 13 min were used to calculate the rate of percutaneous loss (RPL) as follows:

$$RPL = 0.5\,[(V \cdot \Delta_1/T_1) + (V \cdot \Delta_2/T_2)]/ASA,$$

where Δ_1 is the difference between anesthetic concentrations measured at 6–7 min and at the beginning of the interval (vol%/100), Δ_2 is the difference between concentrations at 13 min and 6–7 min (vol%/100), T_1 and T_2 are the duration (min) of the first and second sampling intervals, respectively (i.e., 6 or 7 min), and the variables V and ASA are as above. Values for the rate of percutaneous loss for each agent are expressed as $mL \cdot m^{-2} \cdot min^{-1}$.

Because the rate of percutaneous loss during the first 150 min of elimination correlated with the end-tidal anesthetic concentration (FA), we estimated the percutaneous loss of anesthetics after 150 min from the continuing rate of decay in FA.

We calculated anesthetic uptake (reported separately) as VE·(FI − FM), and elimination as VE·FM.

Total percutaneous losses for sevoflurane and isoflurane were compared during administration and during elimination using a paired *t*-test. Losses for each anesthetic during administration were compared with losses during elimination using a paired *t*-test. All comparisons were made after normalizing losses by the last alveolar value obtained during administration (FA_0). We plotted the rate of percutaneous loss normalized by FA_0 during administration and elimination. We also plotted the rate of percutaneous losses during elimination after normalizing by FA_{-10} (the FA obtained 10 min before the start of a sampling interval).

We then compared the rate of percutaneous loss of

Table 1. Percutaneous Losses of Sevoflurane and Isoflurane During Administration and Elimination of Volatile Agents

Percutaneous loss (mL)	Sevoflurane	Isoflurane
Administration (30 min)		
Absolute values	0.028 ± 0.015	0.042 ± 0.024
Normalized by FA_0	0.035 ± 0.020[a,b]	0.094 ± 0.058[a]
Elimination (total)		
Absolute values	0.339 ± 0.119	0.789 ± 0.332
Normalized by FA_0	0.434 ± 0.199[c]	1.844 ± 0.962
Total loss		
Absolute values	0.367 ± 0.128	0.830 ± 0.345
Loss as % of uptake	0.155 ± 0.045[d]	0.351 ± 0.145

All values are expressed as mean ± SD.

Loss is expressed as absolute values, absolute values normalized by FA_0, and as a percent of uptake.

[a] Significantly different when compared with losses during elimination.

[b] Significantly different from losses for isoflurane during administration.

[c] Significantly different from losses for isoflurane during elimination.

[d] Significantly different from value for isoflurane.

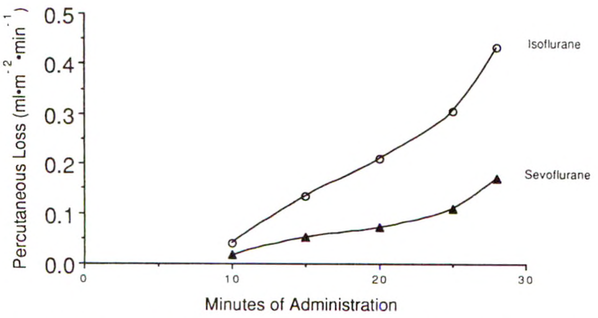


Figure 1. Rates of percutaneous loss (mL·m^{-2}·min^{-1}) for sevoflurane and isoflurane (normalized by their FA_0 values) during administration of the volatile agents.

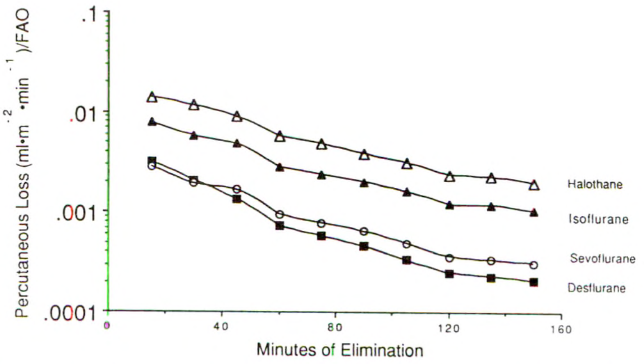


Figure 2. Rates of percutaneous loss (mL·m^{-2}·min^{-1}) for sevoflurane and isoflurane (normalized by their FA_0 values) during elimination in our study. Rates of percutaneous loss (mL·m^{-2}·min^{-1}) of desflurane and halothane (normalized by their FA_0 values) from a previous comparative study are also included (2). Losses for isoflurane in that study served as a control for comparison with our study.

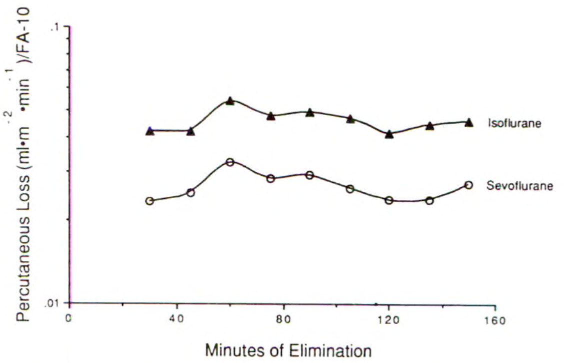


Figure 3. The rate of percutaneous loss (mL·m^{-2}·min^{-1}) during elimination (normalized by FA_{10} values) is constant after the first 30 min of elimination.

sevoflurane relative to desflurane (2) using isoflurane as a control for comparison.

Results

During administration of the volatile agents, total percutaneous loss of isoflurane was significantly greater than loss of sevoflurane (Table 1, Figure 1). Losses during the first 10 min of administration of these agents were inconsequential; they rose thereafter.

Similarly, during elimination, percutaneous loss of isoflurane (normalized by FA_0) was significantly greater (Table 1, Figure 2). Losses during elimination significantly exceeded those during administration for both anesthetics. When normalized by FA_{-10}, the rates of percutaneous loss of each agent reached a plateau after 30 min (Figure 3).

After the first 20 min of elimination, losses of sevoflurane were significantly greater than those previously reported for desflurane (Figure 2).

Discussion

Consistent with previous results (2) suggesting that percutaneous losses of inhaled anesthetics are proportional to anesthetic solubility in blood, we found that losses for isoflurane exceeded those for sevoflurane. Similarly, losses of sevoflurane (blood/gas partition coefficient 0.67 [4]) are greater than losses of desflurane (blood/gas partition coefficient 0.42 [5]). Consistent with our previous results, we found that losses during elimination were greater than those during administration, but that, even when combined, these losses were too small to affect kinetic or metabolic studies based on mass balance.

To raise subcutaneous anesthetic partial pressures to levels sufficient to traverse the skin required a period of 10 min (Figure 1). This temporal delay in anesthetic transfer produced a continuing rise in percutaneous losses during the first 15-min interval after we had discontinued administration of the volatile agents. These findings also confirm those of previous studies (2).

Cullen and Eger (6) suggested that percutaneous losses of anesthetic are diffusion limited. Although differences in molecular weight could affect diffusion characteristics and thus percutaneous losses, sevoflurane and isoflurane (as well as desflurane and halothane) have similar molecular weights. Differences in diffusion are therefore probably related to differences in solvent characteristics of skin.

Intertissue diffusion (7) from dermis to subcutaneous fat has been proposed as a possible cause for differences in percutaneous loss among anesthetics. If this were so, the more blood-soluble anesthetics should have the smallest, not the greatest, percutaneous losses. Because the fat/blood partition coefficient is high for all volatile anesthetics, subcutaneous fat may act as an infinite reservoir for these agents that does not discriminate among them.

On the other hand, the fat solubility of N_2O is small relative to that of the volatile anesthetics, yet the rate of percutaneous loss of N_2O is much greater (1). This suggests that (a) subcutaneous fat limits anesthetic partial pressure in overlying dermis; (b) percutaneous loss is proportional to anesthetic partial pressure in overlying dermis and to diffusion through the epidermis; and (c) diffusion through epidermis is a function of solubility in lean tissues (i.e, the blood/gas partition coefficient).

Percutaneous losses were measured from the forearm and hand, and these values were used to estimate total percutaneous losses. Cutaneous blood flow and thickness of the epidermis vary considerably among different regions of the body (8). These regional differences are likely to affect percutaneous losses of anesthetics. Similarly, regional differences in surface temperature affect cutaneous blood flow and may also influence anesthetic losses. The lack of homogeneity in surface blood flow indicates that our calculations of total percutaneous losses should be considered estimates and not precise values. However, our values do permit an interpretation of relative rates of loss of sevoflurane and isoflurane as well as a comparison with losses for desflurane using isoflurane as a control.

References

1. Stoelting RK, Eger EI II. Percutaneous loss of nitrous oxide, cyclopropane, ether and halothane in man. Anesthesiology 1969;30:278–83.
2. Fassoulaki A, Lockhart SH, Freire BA, et al. Percutaneous loss of I-653, isoflurane and halothane in humans. Anesthesiology 1989;71:A272.
3. Ganong WF. Energy balance, metabolism and nutrition: In: Ganong WF, ed. Review of medical physiology. Los Altos, Calif.: Lange Medical Publications, 1985:228.
4. Strum DP, Eger EI II. Partition coefficients for sevoflurane in human blood, saline, and olive oil. Anesth Analg 1987;66:654–6.
5. Eger EI II. Partition coefficients of I-653 in human blood, saline, and olive oil. Anesth Analg 1987;66:971–3.
6. Cullen BF, Eger EI II. Diffusion of nitrous oxide, cyclopropane, and halothane through human skin and amniotic membrane. Anesthesiology 1972;36:168–73.
7. Perl W, Rackow H, Salanitre S, Wolf GL, Epstein RM. Intertissue diffusion effect for inert fat-soluble gases. J Appl Physiol 1965;20:621–7.
8. Serjrsen P. Blood flow in cutaneous tissue in man studied by washout of radioactive xenon. Circ Res 1969;25:215–29.

ANESTH ANALG
1991;72:216–20

Hypokalemia Before Induction of Anesthesia and Prevention by β_2 Adrenoceptor Antagonism

Evan D. Kharasch, MD, PhD, and T. Andrew Bowdle, MD, PhD

KHARASCH ED, BOWDLE TA. Hypokalemia before induction of anesthesia and prevention by β_2 adrenoceptor antagonism. Anesth Analg 1991;72:216–20.

We have observed that serum potassium levels measured immediately before induction of anesthesia ("preinduction K^+") are often lower than those measured 1–3 days preoperatively ("preoperative K^+"). The purpose of this investigation was to determine, in two studies, the magnitude of this difference and to elucidate the mechanism by which this occurs. In the first study, preinduction K^+ (3.6 ± 0.4 mEq/L, mean ± SD) was significantly lower than K^+ levels measured during routine preoperative testing (4.4 ± 0.4 mEq/L, $n = 47$, $P < 0.001$). Twenty-three patients (49%) had preinduction K^+ levels that were considered hypokalemic (≤3.5 mEq/L), but 22 of these 23 patients had normal preoperative K^+ levels. The second study tested the hypothesis that preinduction decreases in serum K^+ are mediated by β_2-adrenergic receptors. Preinduction K^+ changes were determined in patients given a single preoperative dose of propranolol (β_1/β_2-antagonist), atenolol (β_1-antagonist), or no β-blocker (control). The difference between preoperative and preinduction serum K^+ in patients receiving propranolol (0.1 ± 0.4 mEq/L) was significantly attenuated ($P < 0.02$) compared with the difference in control subjects (0.5 ± 0.4 mEq/L), but was not significantly different from controls in patients pretreated with atenolol (0.3 ± 0.4 mEq/L). These results demonstrate that serum K^+ levels measured intraoperatively just before anesthetic induction are consistently and significantly less than those measured 1–3 days preoperatively. The ability of propranolol but not atenolol to block this change suggests that the acute decrease in K^+ levels was due to β_2-adrenergic receptor stimulation. Therapeutic decisions based on preinduction serum K^+ should consider this phenomenon.

Key Words: IONS, POTASSIUM—preoperative serum levels.

The clinical significance of chronic hypokalemia in patients undergoing anesthesia and surgery is controversial (1–4). It has been the practice of many anesthesiologists to postpone elective procedures in patients with potassium (K^+) levels below normal because of the belief that hypokalemia predisposes these patients to an increased risk of perioperative arrhythmias. Alternatively, practitioners may attempt acute replacement by administration of intravenous K^+. These responses to the presence of hypokalemia are not trivial because the cost and inconvenience of postponing elective surgery are considerable and because intravenous K^+ administration has been associated with a high incidence of hyperkalemia, arrhythmias, and death (5). Recent studies have shown no increased incidence of perioperative arrhythmias in patients with chronic hypokalemia, suggesting that it may be unnecessary to postpone surgery or administer intravenous K^+ (3,4).

The interpretation and clinical significance of chronic hypokalemia appear to be undergoing a change of emphasis as a result of these recent studies. However, the preoperative measurement of serum K^+ concentration has generally not been abandoned. It has been our routine practice to measure K^+ levels, hematocrit, and arterial blood gas tensions at the time of arterial catheterization, before induction of anesthesia. We observed that K^+ values obtained immediately before induction of anesthesia (henceforth called "preinduction K^+") were often considerably lower than values obtained 1–3 days preoperatively (henceforth called "preoperative K^+"), even in patients without an obvious cause for hypokalemia.

Presented in part at the meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989; and at the meeting of the International Anesthesia Research Foundation, Honolulu, Hawaii, March 1990.

Received from the Department of Anesthesiology, University of Washington Medical Center, and the Anesthesiology Service, Veterans Affairs Medical Center, Seattle, Washington. Accepted for publication October 5, 1990.

Address correspondence to Dr. Kharasch, Department of Anesthesiology, RN-10, University of Washington, Seattle, WA 98195.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

The purpose of this investigation was to characterize the acute reduction in serum K^+, measured immediately before induction of anesthesia, and to elucidate the mechanism by which this occurs. Our hypothesis was that the "stress" of the immediate preoperative period, with associated elevation of circulating epinephrine concentrations (6), results in β_2-adrenergic receptor-mediated cellular K^+ uptake (7,8) and a decrease in serum K^+ levels. This hypothesis was tested by attempting to prevent the decrease in serum K^+ by preoperative administration of the β-adrenergic antagonists propranolol or atenolol.

Methods

All protocols were approved by the University of Washington Human Subjects Review Committee, and institutionally approved written informed consent was obtained. The study was divided into two parts. Part 1 was designed to determine the incidence and extent of preinduction hypokalemia. Forty-seven consecutive patients, aged 36–88 yr (63 ± 11, mean ± SD), requiring arterial catheterization for vascular, thoracic, abdominal, or neurologic surgery were studied. Patients received no preoperative sedative-hypnotic or opioid medications. All cases were scheduled to begin at 8 AM. Arterial blood samples were obtained at the time of arterial catheterization in the operating room, just before anesthetic induction, for measurement of preinduction serum K^+. Preoperative serum K^+ was measured in venous samples obtained 1–3 days earlier during routine preoperative testing. Preinduction K^+ levels were compared with preoperative K^+ levels using a paired *t*-test. Hypokalemia was defined as $K^+ \leq 3.5$ mEq/L, and severe hypokalemia was defined as $K^+ \leq 3.0$ mEq/L.

Part 2 was designed to test the hypothesis that the reduction in serum K^+, measured immediately before induction of anesthesia, is mediated by catecholamine stimulation of β_2-adrenergic receptors. Sixty patients aged 28–79 yr (57 ± 15, mean ± SD) undergoing anesthesia for elective vascular, urologic, orthopedic, abdominal, thoracic, or lumbar surgery were studied. Patients receiving chronic β- or calcium channel blockers and those with renal failure, asthma, left ventricular hypertrophy, congestive heart failure, or bradycardia were excluded from study. Patients (20 per group) were randomly assigned to receive propranolol (40 mg orally), atenolol (25 mg orally), or no β-blocker (control) at 5:30 AM, before surgery scheduled for 8 AM. No other anesthetic premedication was administered. Resting heart rate and blood pressure were recorded the evening before surgery and upon arrival in the operating room. The serum K^+ level was measured in venous blood samples obtained in the operating room immediately before anesthetic induction and was compared with the preoperative venous serum K^+ values measured 1–3 days previously.

Serum K^+ levels were measured by the medical center clinical laboratory using standard ion-specific electrode techniques. In part 1, preoperative venous samples were collected in standard red-top laboratory tubes and arterial samples were collected in heparinized plastic syringes. Two instruments were used to measure K^+. Standard clinical laboratory methods were used to assure that the results obtained were comparable for each instrument. We independently verified the reproducibility and comparability of the assays by running samples with and without heparin simultaneously on the two instruments. In part 2, the analytical methods were simplified by collecting all samples in red-top tubes and using a single instrument for all K^+ measurements. All results are expressed as mean ± SD. Repeated measures or one-way analysis of variance followed by the Student–Newman–Keuls test was used to test for significant differences between preoperative and preinduction K^+ levels and heart rate.

Results

Part 1

Mean serum K^+ levels determined at the time of arterial line placement, immediately before induction of anesthesia (3.6 ± 0.4 mEq/L), were significantly lower than mean serum K^+ levels measured during routine preoperative testing (4.4 ± 0.4 mEq/L, $P < 0.001$). The mean interval between preoperative and preinduction measurements was 44 ± 34 h. Preinduction K^+ was lower than preoperative K^+ in 44 of 47 patients (Figure 1). Twenty-three patients (49%) had preinduction K^+ levels that were considered hypokalemic by traditional criteria (≤3.5 mEq/L), and five were severely hypokalemic (<3.0 mEq/L, Table 1). Twenty-two of these 23 hypokalemic patients, however, had preoperative K^+ levels that were considered normal. The results were not influenced by the use of preoperative cathartic bowel preparations ($n = 2$) or chronic use of diuretics with ($n = 7$) or without ($n = 16$) oral K^+ supplementation (Table 2).

Part 2

Preinduction heart rate was significantly less than preoperative heart rate in patients receiving atenolol

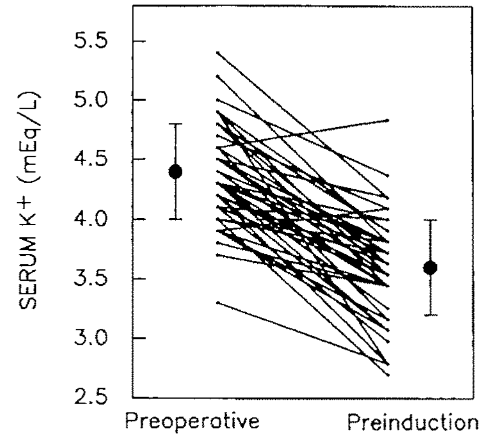


Figure 1. Individual and mean (±SD) preoperative and preinduction serum K$^+$ levels in 47 patients.

Table 1. Frequency of Hypokalemia

Serum potassium (mEq/L)	Preoperative *n*	Preoperative %	Preinduction *n*	Preinduction %
≥3.6	46	98	24	51
3.1–3.5	1	2	18	38
≤3.0	0		5	11

Table 2. Influence of Diuretic Use on Perioperative Potassium

Patients	*n*	Serum potassium (mEq/L) Preoperative	Serum potassium (mEq/L) Preinduction
All	47	4.4 ± 0.4	3.6 ± 0.4^a
No diuretics	31	4.3 ± 0.4	3.6 ± 0.4^a
Diuretics	16	4.6 ± 0.5	3.9 ± 0.1^a
Diuretics + oral KCl supplements	7	4.7 ± 0.4	3.8 ± 0.7^b

[a] Significantly different from preoperative potassium ($P < 0.001$).
[b] Significantly different from preoperative potassium ($P < 0.005$).

(75 ± 14 vs 62 ± 10, $P < 0.001$) or propranolol (77 ± 11 vs 62 ± 11, $P < 0.001$), demonstrating adequacy of β-blockade. Blood pressure was not significantly affected. Figure 2 shows the influence of β-blocker pretreatment on the decrease in preinduction serum K$^+$. The mean interval between preoperative and preinduction measurements was 34 ± 26 h. In the control group (no β-blocker), preinduction K$^+$ (3.9 ± 0.4 mEq/L) was significantly less than preoperative K$^+$ (4.4 ± 0.3 mEq/L, $P < 0.001$). In patients receiving 40 mg propranolol on the morning of surgery, preinduction K$^+$ was not significantly different from preoperative K$^+$ (4.0 ± 0.4 vs 4.1 ± 0.4 mEq/L, $P > 0.5$). The difference between preoperative and preinduction serum K$^+$ levels in propranolol-treated patients (0.1 ± 0.4 mEq/L) was significantly less than that in control patients (0.5 ± 0.4 mEq/L, $P < 0.02$). In contrast, in patients receiving 25 mg atenolol, preinduction K$^+$ did decline significantly (3.9 ± 0.3 vs 4.2 ± 0.3 mEq/L, $P < 0.02$), and the difference between preoperative and preinduction serum K$^+$ levels (0.3 ± 0.4 mEq/L) was not significantly different from that observed in control subjects ($P > 0.2$).

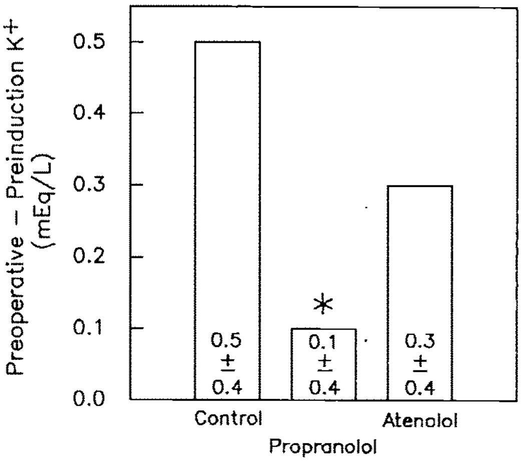


Figure 2. Influence of oral atenolol or propranolol administration on the preinduction decrease in serum K$^+$ levels. Results are shown as the mean difference (±SD) between preoperative and preinduction venous serum K$^+$ levels. There were 20 patients in each group. The *asterisk* denotes a significant difference between controls and patients pretreated with a β-receptor antagonist ($P < 0.02$).

Discussion

Serum K$^+$ levels measured immediately before induction of anesthesia were consistently and significantly lower than levels determined 1–3 days previously during routine preoperative testing. Serum K$^+$ levels declined in 94% of patients in part 1 and in 75% of patients not receiving β-blockers in part 2 of this study. Applying conventional criteria of hypokalemia (K$^+$ ≤ 3.5 mEq/L), almost 50% of the patients in the first study would have been considered hypokalemic based on measurement of preinduction K$^+$, yet all but one of these patients were normokalemic according to routine preoperative tests. The change in serum K$^+$ was not explained by any apparent source of K$^+$ loss such as cathartic bowel preparations or diuretics. These results are similar to those of Hirsch et al. who found serum K$^+$ values measured before induction to be significantly lower than plasma K$^+$ measured 12–36 h preoperatively (4). The average decrease (0.28 mEq/L) in the study by Hirsch et al. was smaller than that observed in the present study

(0.5–0.8 mEq/L), perhaps because 108 of 447 patients were receiving β-blockers (see below).

Although part 1 of this investigation compared preoperative venous K^+ with preinduction arterial K^+, we do not believe that the site of blood sampling significantly affected the results. Arterial and venous K^+ concentrations do not differ significantly (9). Furthermore, both preoperative and preinduction K^+ levels were measured in venous blood samples in part 2, confirming the results of part 1.

Part 2 of this investigation tested the hypothesis that the decline in serum K^+ before induction of anesthesia was due to a β_2-receptor-mediated event. There were several theoretical reasons to suspect this mechanism. Fell et al. found increased plasma epinephrine levels in the immediate preoperative period even in premedicated patients (6). Numerous investigations have shown that epinephrine produces hypokalemia by a shift of extracellular K^+ into cells, mainly in liver and skeletal muscle (10), mediated by β_2-receptor stimulation (7,8). The hypokalemia is not the result of altered K^+ excretion (11,12). Epinephrine infusion that produced a twofold to threefold increase in plasma epinephrine levels resulted in a 0.2 mEq/L decrease in serum K^+, and a 10–15-fold increase in plasma epinephrine levels caused a 0.4–0.9 mEq/L decrease (13,14). The β_2-specificity of this epinephrine effect was shown by the ability of a β_2-selective antagonist to prevent the decrease in K^+ levels (14). Furthermore, the selective β_2-agonists salbutamol and terbutaline cause a decrease in serum K^+ concentration (12,15). Propranolol and other nonselective β-antagonists completely prevent changes in serum K^+ concentration caused by epinephrine and selective β_2-agonists, whereas atenolol and other more β_1-selective antagonists only partially block these effects (13,16–20).

The results of part 2 of this investigation suggest that the decrease in K^+ measured immediately before induction was due to a β_2-receptor-mediated event. Propranolol, a nonselective β_1/β_2-antagonist, completely prevented the hypokalemia observed in the control group, whereas the selective β_1-antagonist atenolol failed to significantly prevent the preinduction hypokalemia. Atenolol slightly attenuated the change in K^+ but did not prevent it completely. This is in agreement with previous studies that show that selective β_1-antagonists (with slight β_2-antagonist activity) only partially prevent the hypokalemic effect of epinephrine (13,16,17).

The most likely explanation for β_2-receptor stimulation in this study is stress-induced catecholamine release. Although catecholamines were not measured in the present investigation, elevation of circulating catecholamines has been demonstrated previously for a wide variety of stressful physiological and psychological conditions (21). Fell et al. have shown that epinephrine levels increase significantly immediately before induction of anesthesia (6). Furthermore, the fact that β_2-blockade prevents the decrease in preinduction K^+ strongly implies that epinephrine mediates preinduction hypokalemia. Explanations other than β_2-receptor stimulation from stress-induced catecholamine release may be considered but are less likely (22–24). Metabolic or respiratory alkalosis may cause acute hypokalemia, but in the present studies measurements of arterial blood gas tensions performed along with K^+ measurements on intraoperative blood samples showed no acid-base disturbances (pH 7.42 ± 0.04, $P\text{co}_2$ 40 ± 6 mm Hg). Starvation may produce hypokalemia, but a single overnight fast has no effect on serum K^+ levels (25,26). An association between hypokalemia and postoperative hypothermia has been noted (27,28), but we do not suspect significant preinduction hypothermia in the patients we studied. A diurnal variation in serum K^+ with a morning trough could explain our results, but most authors find no significant diurnal variation in plasma K^+ (29,30). One recent report did suggest a diurnal variation, but with serum K^+ levels being found to *peak* in the morning (31). Our data showed no cyclic relationship between the preoperative to preinduction measurement interval and the preinduction decrease in serum K^+ (data not shown), evidence that diurnal variation in serum K^+ cannot explain our results. None of the patients studied had abnormal losses of gastric fluid.

We have shown that serum K^+ levels measured just before induction of anesthesia are consistently and significantly less than those measured 1–3 days preoperatively. This preinduction hypokalemia was prevented by administration of propranolol but not atenolol, suggesting that the acute decrease in K^+ was due to β_2-receptor stimulation and thus a shift of extracellular K^+ into cells. Therapeutic decisions based on preinduction serum K^+ concentrations should consider this phenomenon. Based on this investigation, we suggest that the decision to cancel surgery or administer supplemental K^+ should not be made solely on the basis of serum K^+ levels measured in the period immediately preceding surgery.

References

1. Wong KC. Hypokalemia and dysrhythmias. J Cardiothorac Anesth 1989;3:529–31.
2. McGovern B. Hypokalemia and cardiac arrhythmias. Anesthesiology 1985;65:127–9.

3. Vitez TS. Chronic hypokalemia and intraoperative dysrhythmias. Anesthesiology 1985;63:130–5.
4. Hirsch IA, Tomlinson DL, Slogoff S, Keats AS. The overstated risk of preoperative hypokalemia. Anesth Analg 1988;67:131–6.
5. Lawson DH. Adverse reactions to potassium chloride. Q J Med 1974;171:433–40.
6. Fell D, Derbyshire DR, Maile CJD, et al. Measurement of plasma catecholamine concentrations. An assessment of anxiety. Br J Anaesth 1985;57:770–4.
7. Struthers AD, Reid JL. The role of adrenal medullary catecholamines in potassium homeostasis. Clin Sci 1984;66:377–82.
8. Brown MJ. Hypokalemia from beta-2-receptor stimulation by circulating epinephrine. Am J Cardiol 1985;56:3D–9D.
9. Hastings RH. Arteriovenous potassium ion difference in critically ill patients (abstract). Anesth Analg 1990;70:S149.
10. Vick RL, Todd EP, Luedke DW. Epinephrine-induced hypokalemia: relation to liver and skeletal muscle. J Pharmacol Exp Ther 1972;181:139–46.
11. Smith SK, Thompson D. The effect of intravenous salbutamol upon plasma and urinary potassium during premature labour. Br J Obstet Gynaecol 1977;84:344–7.
12. Leitch AG, Clancy LJ, Costello JF, Flenley DC. Effect of intravenous infusion of salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal men. Br Med J 1976;1:365–7.
13. Struthers AD, Reid JL, Whitesmith R, Rodger JC. Effect of intravenous adrenaline on electrocardiogram, blood pressure, and serum potassium. Br Heart J 1983;49:90–3.
14. Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta-2-receptor stimulation by circulating epinephrine. N Engl J Med 1983;309:1414–9.
15. Moravec MA, Hurlbert BJ. Hypokalemia associated with terbutaline administration in obstetrical patients. Anesth Analg 1980;59:917–20.
16. Massara F, Tripodina A, Rotunno M. Propranolol block of epinephrine-induced hypokaliaemia in man. Eur J Pharmacol 1970;10:404–7.
17. Vincent HH, Man in't Veld AJ, Boomsma F, Schalekamp MADH. Prevention of epinephrine-induced hypokalemia by nonselective beta blockers. Am J Cardiol 1985;56:10D–4D.
18. Berend N, Marlin GE. Characterization of β-adrenoceptor subtype mediating the metabolic actions of salbutamol. Br J Clin Pharmacol 1978;5:207–11.
19. Smith SR, Kendall MJ, Worthington DJ, Holder R. Can the biochemical responses to a $\beta 2$-adrenoceptor stimulant be used to assess the selectivity of β-adrenoceptor blockers? Br J Clin Pharmacol 1983;16:557–60.
20. Strauss MH, Reeves RA, Smith DL, Leenen FHH. The role of cardiac beta-1 receptors in the hemodynamic response to a beta-2 agonist. Clin Pharmacol Ther 1986;40:108–15.
21. Cryer PE. Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. N Engl J Med 1980; 303:436–44.
22. Sterns RH, Cox M, Feig PU, Singer I. Internal potassium balance and the control of the plasma potassium concentration. Medicine 1981;60:339–54.
23. Cox M. Potassium homeostasis. Med Clin North Am 1981;65: 363–84.
24. Nardone D, McDonald B, Girard D. Mechanisms in hypokalemia. Medicine 1978;57:435–46.
25. Lawlor T, Wells DG. Metabolic hazards of fasting. Am J Clin Nutr 1969;22:1142–9.
26. Lawlor T, Wells DG. Fasting as a treatment of obesity. Postgrad Med J 1971;47(Supp):452–8.
27. Koht A, Cane R, Cerullo LJ. Serum potassium levels during prolonged hypothermia. Intensive Care Med 1983;9:275–7.
28. Boelhouwer RU, Bruining HA, Ong GL. Correlations of serum potassium fluctuations with body temperature after major surgery. Crit Care Med 1987;15:310–2.
29. Vagnucci AI, Wesson LG Jr. Diurnal cycle of renal hemodynamics and excretion of chloride and potassium in hypertensive subjects. J Clin Invest 1964;43:522.
30. Wesson Jr LG. Electrolyte excretion in relation to diurnal cycles of renal function. Medicine 1964;43:547–92.
31. Solomon R, Dubey A. Diurnal variation in serum potassium. Clin Pharmacol Ther 1989;45:155.

Cardiovascular, Respiratory, and Analgesic Effects of Fentanyl in Unanesthetized Rhesus Monkeys

Nancy A. Nussmeier, MD, James L. Benthuysen, MD, Eugene P. Steffey, DVM, John H. Anderson, DVM, Earl E. Carstens, PhD, John H. Eisele, Jr, MD, and Theodore H. Stanley, MD

NUSSMEIER NA, BENTHUYSEN JL, STEFFEY EP, ANDERSON JH, CARSTENS EE, EISELE JH Jr, STANLEY TH. Cardiovascular, respiratory, and analgesic effects of fentanyl in unanesthetized rhesus monkeys. Anesth Analg 1991;72:221–6.

To determine the suitability of the rhesus monkey as a model for investigation of opioids, we examined the analgesic, respiratory, and cardiovascular effects of fentanyl in six adult male rhesus monkeys. Fentanyl was administered in sequential bolus injections of 2, 4, 16, 64, and 128 μg/kg, with 10 min between each dose. Arterial plasma fentanyl concentrations and blood gas tensions were measured 3 and 9 min after each dose and 1, 2, 5, 20, 60, and 120 min after the final dose. At the same time periods, mean systemic arterial, pulmonary arterial, central venous, and pulmonary capillary wedge pressures, cardiac output, heart rate, and respiratory rate were measured. Analgesia was quantified as the time required for tail withdrawal from a standardized noxious stimulus. Tail latency response time increased significantly after the 4-μg/kg dose (plasma fentanyl concentration = 2.7 ± 0.9 ng/mL). Maximum tail latency response time was attained after the 64-μg/kg dose (43.4 ± 26.0 ng/mL). Respiratory rate decreased significantly after the 2-μg/kg dose, and Pa_{CO_2} *increased significantly after the 4-μg/kg dose. All animals became apneic, requiring tracheal intubation and controlled ventilation, after the 64-μg/kg dose. Also, mean arterial pressure and cardiac output decreased significantly after the 64-μg/kg dose. There were no other significant cardiovascular changes. Peak plasma fentanyl concentration after the 128-μg/kg dose was 117.0 ± 49.6 ng/mL. It appears that plasma concentrations of approximately 40 ng/mL are sufficient to reach the full cardiovascular, respiratory, and analgesic effects of fentanyl in the rhesus monkey. Significant respiratory and analgesic effects are evident at concentrations as low as 3 ng/mL. These effects of fentanyl are similar to those previously reported in humans.*

Key Words: ANESTHETICS, INTRAVENOUS, FENTANYL—pharmacologic effects in rhesus monkeys.

Synthetic opiates have largely replaced morphine as agents of choice for intraoperative analgesia (1). Of these, fentanyl has emerged as a standard against which similar drugs are frequently compared. However, the ability of these drugs to act as sole anesthetics remains controversial. Case reports of awareness during high-dose fentanyl anesthesia prompted related laboratory studies that attempt to quantify the anesthetic properties of these opioids (2–4).

One approach to this problem has been to perform MAC reduction studies, in which the ability of an opiate to replace an inhalation anesthetic is quantified (5). These studies have been performed in the rat (6,7) and dog (5,8). However, number and type of opiate receptors and physiologic responses to opiates differ among species. Therefore, many laboratory investigations may not be directly applicable to humans (9,10). For example, fentanyl administration in unanesthetized dogs produces respiratory depression but not apnea even after as much as 3000 μg/kg (11,12).

The phylogenetic proximity of primates to humans (13) suggests that primates may be of greater utility for investigating the actions of fentanyl and other synthetic opioids than other mammals (11). In vivo positron tomographic imaging of opiate receptors in humans and baboons using a fentanyl derivative, carfentanil, demonstrates a very similar pattern of opiate receptor distribution (14). When a simple dose-response comparison using carfentanil is performed,

---

Received from the Department of Anesthesia and the California Primate Research Center, University of California, Davis, California. Accepted for publication October 5, 1990.

Address correspondence to Dr. Nussmeier, Department of Anesthesia, University of California, 513 Parnassus Avenue, San Francisco, CA 94143-0648.

©1991 by the International Anesthesia Research Society

apnea and anesthesia occur in the rhesus monkey at doses that are 1/100th the dose that produces analgesia and sedation, but limited respiratory depression, in the dog (15). Reports such as these suggest the usefulness of an examination of the actions of fentanyl in the nonhuman primate. In this investigation, we examined the cardiovascular, respiratory, and analgesic responses of the unanesthetized rhesus monkey to sequentially increasing doses of fentanyl.

Methods

The protocol was reviewed and approved by the University of California at Davis Animal Care and Use Administrative Committee and the University of California at Davis Primate Center Animal Care Committee. Six adult male rhesus monkeys (mean age, 12.8 ± 3.9 yr; mean weight, 14.1 ± 2.3 kg) were studied. Animals were pretrained to tolerate prolonged chair restraint using the methods of Golub and Anderson (16). None of the animals had received opiate analgesics within 3 mo of the study.

On the morning of study, a spontaneously breathing monkey was briefly anesthetized with isoflurane in 100% oxygen delivered initially by a close-fitting hood. The animal's trachea was intubated (without the use of muscle relaxants), and anesthesia was maintained with isoflurane in oxygen. Peripheral intravenous and femoral artery cannulae (20 gauge) were inserted, and a 5F pulmonary artery catheter (American Edwards) was introduced into the femoral vein and positioned in the right pulmonary artery with the aid of fluoroscopy. The tracheal tube was then removed and the monkey allowed to recover for 4 h while sitting in a restraint chair before the beginning of the fentanyl study. A continuous infusion of 0.95% saline was administered throughout the recovery period and subsequent study period at a rate calculated to deliver maintenance fluid requirements.

Each animal received fentanyl as five bolus injections according to a fixed dosage schedule: 2, 4, 16, 64, and 128 μg/kg fentanyl (cumulative dose, 214 μg/kg), each dose being administered over 1 min with 10 min between doses. Arterial blood samples were obtained before the study began, 3 and 9 min after each fentanyl dose, and 1, 2, 5, 20, 60, and 120 min after the final dose. Plasma specimens were stored at −70°C until an analysis of fentanyl was performed using a radioimmunoassay technique (Janssen Pharmaceutica). Withdrawn blood was replaced with three times the volume of 0.95% saline.

The electrocardiogram (lead II) as well as arterial systemic, pulmonary arterial, and central venous pressures were continuously recorded on an eight-channel Grass recorder. Triplicate thermodilution cardiac output determinations and pulmonary capillary wedge pressure measurements were made before beginning the study and again within 1 min of obtaining each arterial sample for measurement of plasma fentanyl levels.

Respiration was continually observed by an experienced veterinarian (E.P.S.) who measured respiratory rate and behavior. Oxygen ($F_{IO_2} > 0.50$) was administered via a clear plastic hood before administration of fentanyl and throughout the study. Oxygen saturation was measured continuously with a Nellcor pulse oximeter attached to a shaved portion of the monkey's tail. In addition, blood gas tensions were measured in arterial samples also used for measuring plasma fentanyl levels. With the onset of a decrease in oxygen saturation below 92%, unresponsiveness to visual stimuli, or apnea, the hood was removed and the monkeys were intubated with a cuffed 5.0-mm endotracheal tube (without the use of muscle relaxants) and controlled ventilation initiated with 100% oxygen. Ventilation was adjusted to maintain normocarbia ($Pa_{CO_2} \approx 40$ mm Hg) as assessed by measurement of arterial blood gas tensions.

The analgesic effect of fentanyl was quantified as the time required for the animal to withdraw his tail after application of a noxious thermal stimulus (tail-flick latency). The freely moving shaved tail was placed in an intense beam of light; the light intensity was adjusted to produce a tail withdrawal time of 3.2–4.4 s during the control period. With the administration of fentanyl, a timer circuit automatically cut off the light after 10 s if there was no tail flick, because cutaneous thermal damage is detectable at exposures exceeding 10 s. During the study period, testing of the level of analgesia was performed at the same time that arterial samples were obtained.

Cardiovascular, respiratory, and analgesic data were analyzed for significant changes compared to control values using analysis of variance for repeated measures with the Fisher protected least significant difference test to determine significant differences after each sequential fentanyl dose. A *P* value of 0.05 was considered to be significant. All values are reported as mean ± SD.

Results

Plasma fentanyl concentrations, measured 3 and 9 min after each injection, were both dose and time

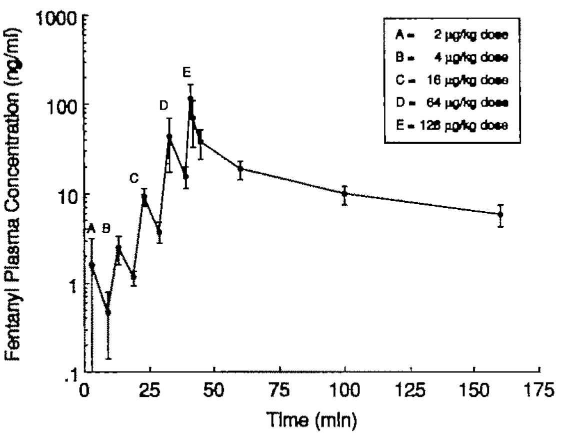


Figure 1. Fentanyl plasma concentrations (mean ± SD), measured 3 and 9 min after each sequential dose of fentanyl (2, 4, 16, and 64 µg/kg). The final dose of fentanyl (128 µg/kg) was administered 40 min after the initial dose; plasma concentrations were measured at 1, 2, 5, 20, 60, and 120 min after the final dose. Ordinate: fentanyl concentrations in logarithmic scale.

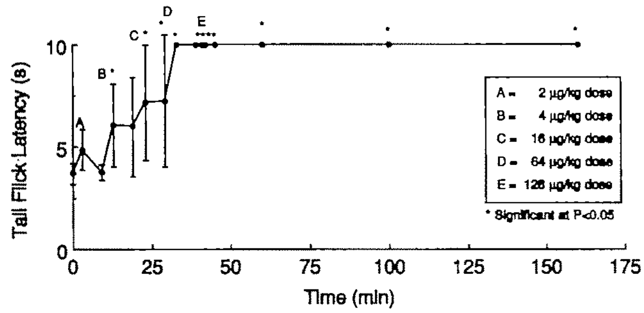


Figure 2. Tail-flick latency response times (mean ± SD), measured 3 and 9 min after each sequential dose of fentanyl (2, 4, 16, and 64 µg/kg). Response time exceeded the maximum allowable time of 10 s after administration of the 64-µg/kg dose and throughout the remainder of the study.

dependent (Figure 1). Tail latency response times increased significantly from 3.7 ± 0.5 to 6.1 ± 2.0 s after administration of the 4-µg/kg dose, corresponding to plasma fentanyl concentrations of 2.7 ± 0.9 ng/mL (Figures 1 and 2). With increasing incremental fentanyl doses, tail-flick latency response times increased until the cutoff point of 10 s was attained after administration of the 64-µg/kg dose (86-µg/kg cumulative dose) in all animals. At this time, plasma fentanyl concentrations were 43.4 ± 26.0 ng/mL. Tail latency response times exceeded 10 s after administration of the final dose (128 µg/kg) and throughout the 120-min recovery period.

Concomitant with onset of analgesia, respiratory rate decreased significantly after administration of the 2-µg/kg dose, whereas $Paco_2$ increased significantly after the 4-µg/kg dose (Figure 3). All animals were apneic and required intubation after the same fentanyl dose that produced profound analgesia

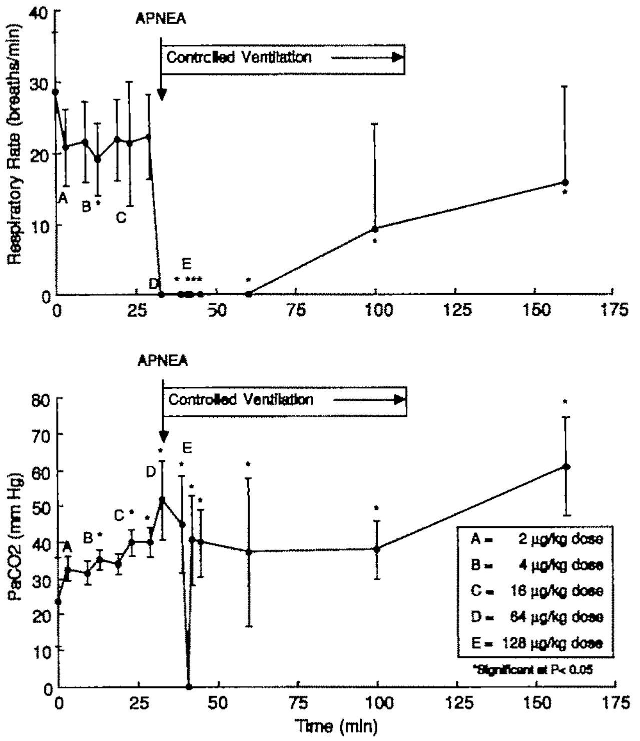


Figure 3. Respiratory rate and $Paco_2$, measured 3 and 9 min after each sequential dose of fentanyl (2, 4, 16, and 64 µg/kg) and at 1, 2, 5, 20, 60, and 120 min after the final fentanyl dose (128 µg/kg), which was administered 40 min after beginning the study. The *arrow* denotes onset of apnea after the 64-µg/kg dose, followed by intubation and controlled ventilation of all animals for a duration of 79 ± 22 min. All values are reported as mean ± SD.

(64 µg/kg). At the time of intubation, the animals were unresponsive to visual or tactile stimuli.

After administration of lower fentanyl doses (2, 4, and 16 µg/kg), there were no significant cardiovascular changes (Figure 4 and 5). After the 64-µg/kg dose, mean arterial pressure decreased significantly by approximately 30% and remained significantly lower than control throughout the 120-min recovery period (Figure 4). Also, after the 64-µg/kg dose of fentanyl, cardiac output decreased significantly by approximately 30% for at least 60 min. Heart rate decreased approximately 10% after the initial fentanyl dose (2 µg/kg) and did not decline further after subsequent doses; this decrease was not significant. Stroke volume did not change until administration of the 128-µg/kg dose, then decreased by approximately 15%, contributing to the significant decrease in cardiac output. Pulmonary arterial, central venous, and pulmonary capillary wedge pressures did not change significantly throughout the study (Figure 5). Calculated values for systemic vascular resistance did not change significantly after fentanyl administration, although a significant decrease was evident 2 h after

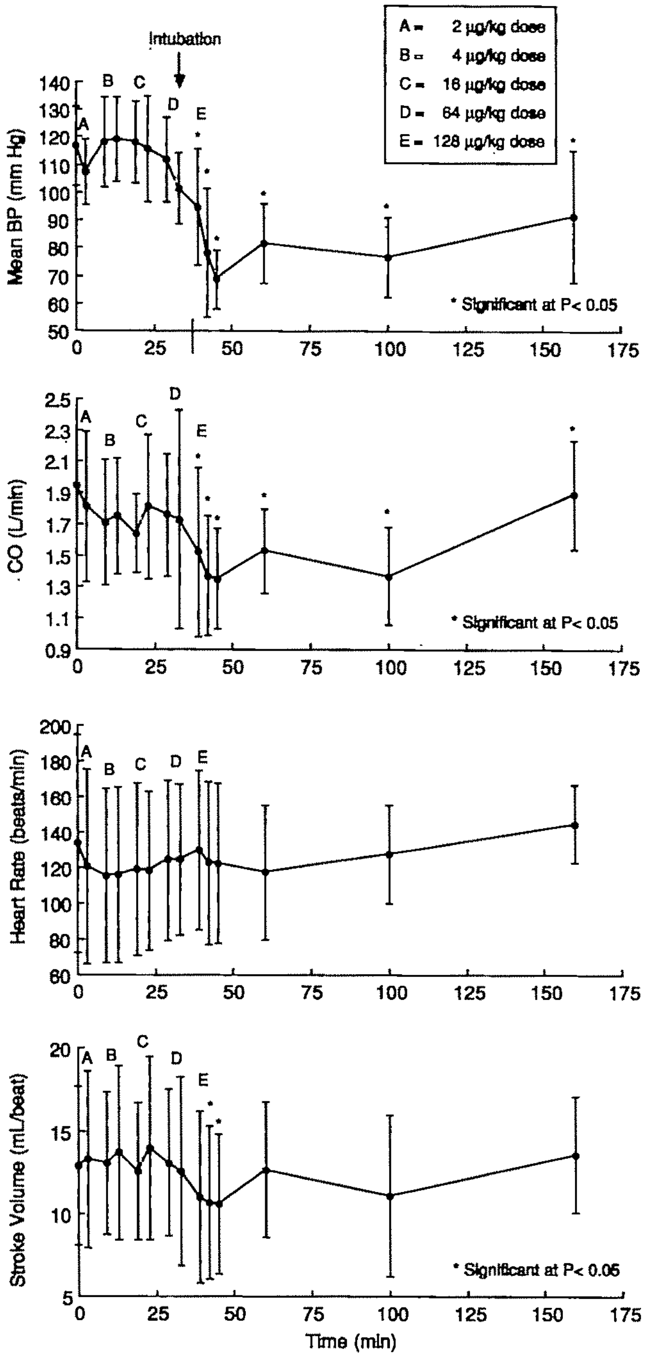


Figure 4. Mean arterial blood pressure (BP), cardiac output (CO), heart rate, and stoke volume, measured 3 and 9 min after each sequential dose of fentanyl (2, 4, 16, and 64 µg/kg) and at 1, 2, 5, 20, 60, and 120 min after the final fentanyl dose (128 µg/kg), which was administered 40 min after beginning the study. The *arrow* indicates the time at which all animals needed to be intubated, after administration of the 64-µg/kg dose of fentanyl. All values are reported as mean ± SD.

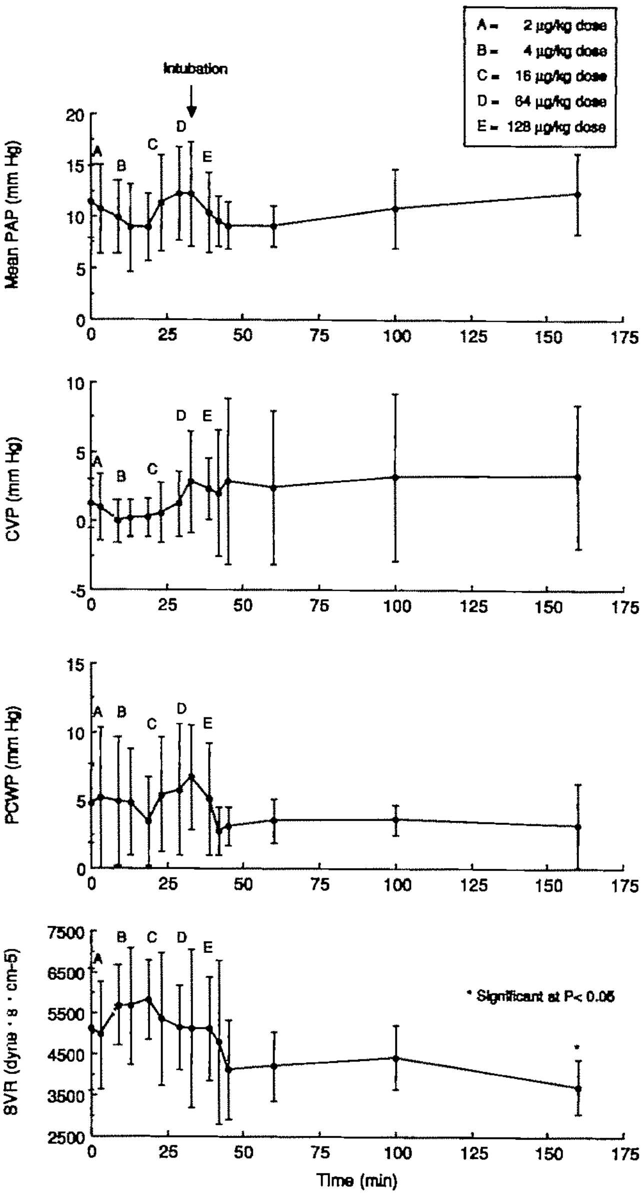


Figure 5. Mean pulmonary arterial pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR), measured 3 and 9 min after each sequential dose of fentanyl (2, 4, 16, and 64 µg/kg) and at 1, 2, 5, 20, 60, and 120 min after the final fentanyl dose (128 µg/kg), which was administered 40 min after beginning the study. The *arrow* indicates the time that all animals were intubated, after administration of the 64-µg/kg dose of fentanyl. All values are reported as mean ± SD.

the final dose. There was no change in any cardiovascular variable as a consequence of intubation.

Fentanyl plasma concentrations decreased quickly from the peak concentration (117.0 ± 49.6 ng/mL) measured 1 min after administration of the final dose to 70.7 ± 37.7 ng/mL after 2 min, then to 37.7 ± 13.5 ng/mL after 5 min. A slower decline to 5.8 ± 1.5 ng/mL occurred during the next 115 min (Figure 1). Cardiac output returned to control levels by 120 min after the final fentanyl injection, when plasma fentanyl concentrations were 5.8 ± 1.5 ng/mL, but mean arterial pressure remained significantly decreased (Figure 4). Spontaneous ventilation resumed 72 ± 22 min after the final fentanyl injection; duration of intubation was 79 ± 22 min. All animals were breathing spontaneously and were extubated at the conclusion of the study (120 min after the final fentanyl dose). However, Pa_{CO_2} remained increased in all animals after extubation (Figure 3) and four of the six animals required naloxone to counteract these effects of fentanyl (plasma concentrations = 5.8 ± 1.5 ng/mL). Also, tail latency response times still exceeded 10 s at the conclusion of the study.

Therefore, it appears that plasma fentanyl concentrations of approximately 40 ng/mL are sufficient to reach the full analgesic, respiratory, and cardiovascular effects in the rhesus monkey. Significant respiratory and analgesic effects are evident at concentrations as low as 3 ng/mL.

Discussion

The cardiovascular, respiratory, and analgesic effects of fentanyl are well characterized in humans (1, 17–22). In other mammals, the dosage requirements and responses to opiates differ from humans (5–8,11,12). Most notable are differences in the respiratory and analgesic effects of fentanyl in the dog and in humans (11,12). Spontaneous ventilation remains intact in dogs, even after extremely high doses (3000 μg/kg) of fentanyl, whereas humans develop apnea after receiving 5–40 μg/kg (1). If fentanyl can produce "anesthesia" in the dog, requirements vary enormously and duration of anesthesia is brief (12).

In our study of large male rhesus monkeys, the plasma fentanyl concentration producing analgesia, approximately 3 ng/mL, is comparable to that reported in humans (23). Also, respiratory depression detectable by significant decreases in respiratory rate and increases in Pa_{CO_2} was evident at the same threshold plasma fentanyl concentration, 2–3 ng/mL, in this investigation and in humans (19,24). In rhesus monkeys at rest, normal values for respiratory rate (38 ± 6 breaths/min) are similar to baseline values obtained in the present study (29 ± 9 breaths/min) (25). However, because baseline Pa_{CO_2} values were lower in this study (24 ± 12 mm Hg) compared with normal values (42 ± 1 mm Hg), our monkeys may have been hyperventilating before administration of fentanyl (25).

Also, baseline cardiovascular parameters obtained in this study were similar to published normal values for heart rate (143 ± 31 beats/min), mean arterial pressure (113 ± 13 mm Hg), and cardiac output (1.8 ± 0.7 L/min) in rhesus monkeys (25). As with humans, mean arterial pressure, cardiac output, stroke volume, pulmonary arterial and central venous pressures, and systemic vascular resistance were not significantly changed at lower fentanyl plasma concentrations (<40 ng/mL) (1,17–22). The significant decrease in mean arterial pressure and cardiac output at concentrations >40 ng/mL is different from humans. This difference may be explained by the absence of surgical stimulation in this study or by the sitting position of the monkeys instead of the supine position in all reported human studies (17–22). A less likely possibility for this difference is the intermittent positive pressure ventilation that was employed in the monkeys after administration of the 64-μg/kg fentanyl dose, because positive pressure ventilation is also required in humans after similar large doses.

Opiate receptors mediate the diverse actions of the endogenous opioid peptides as well as exogenous opiate drugs. In a given species, receptor-mediated opiate effects should attain a maximum that represents the upper functional limit of the opiate receptor system in that species, so long as potentially toxic side effects, such as apnea, are prevented (11). In this investigation, the maximum analgesic, cardiovascular, and respiratory actions of fentanyl were attained in rhesus monkeys at plasma fentanyl concentrations of approximately 40 ng/mL, comparable to the concentration required to produce maximum effects in humans (21,22). It is possible that the various opiate receptors (μ, δ, κ) are similar in number and location within the central nervous system in subhuman compared with human primates (14).

Extubation was possible much sooner in the rhesus monkey, 2 h after the final dose, than would be possible in humans after similar large total doses (214 μg/kg) of fentanyl, although the use of naloxone was required in four of six monkeys. Also, it was not, of course, possible to assess whether the monkeys experienced any residual awareness after administration of these large doses (2–4). However, all animals were unresponsive to visual and tactile stimuli and were exhibiting profound analgesia. Side effects, such as muscle rigidity (1,24), nausea or vomiting (26,27), and myoclonus (17,28), have been reported in humans after administration of large doses of fentanyl. These side effects were not noted in our six rhesus monkeys. It is likely that the number of monkeys studied was too small to note a side effect as rare as myoclonus. However, muscle rigidity and vomiting are common after narcotic administration in humans. It is likely that species difference accounts for the absence of these latter side effects in the rhesus monkey. The rat remains the animal of choice for investigation of muscle rigidity associated with opiate administration (29). The inability to determine definitely whether awareness occurs and the absence of some side effects are limitations of the rhesus monkey model for investigation of clinically useful narcotic drugs.

Despite these limitations, the rhesus monkey appears to be a good model for investigating the effects of opiates in humans. The potential toxicity of large doses of opiates in current clinical use could be evaluated in the monkey. A more important application may be the evaluation of new opiates (e.g., carfentanil) and new methods of administration (e.g., inhalation in a nebulized form or transcutaneous absorption after application of a skin patch) before preclinical drug trials in healthy human volunteers. However, results of studies examining such alternate methods of drug administration in primates must be cautiously interpreted because we noted differences between the rhesus monkey and humans in fentanyl kinetics, particularly in the duration of requirement for assisted ventilation. Also, the usefulness of this primate model in evaluation of drugs with molecular structures differing from that of fentanyl is unknown.

The authors gratefully acknowledge the assistance of Richard W. Martucci, Darcy D. Quam, Michael J. Woliner, and Feng Yu (Freda) Hwang in performance of the technical aspects of this study.

References

1. Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. Anesthesiology 1984;61:731–55.
2. Mark JB, Greenberg LM. Intraoperative awareness and hypertensive crisis during high dose fentanyl-diazepam anesthesia. Anesth Analg 1983;62:698–700.
3. Hilgenberg JC. Intraoperative awareness during high-dose fentanyl-oxygen anesthesia. Anesthesiology 1981;54:341–3.
4. Mummaneni N, Rao TLK, Montoya A. Awareness and recall with high-dose fentanyl-oxygen anesthesia. Anesth Analg 1980;59:948–9.
5. Murphy MR, Hug CC. The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 1982;57:485–8.
6. Hecker BR, Lake CL, DiFazio CA, Moscicki JC, Engle JS. The decrease of the minimum alveolar anesthetic concentration produced by sufentanil in rats. Anesth Analg 1983;62:987–90.
7. Lake CL, DiFazio CA, Moscicki JC, Engle JS. Reduction in halothane MAC: comparison of morphine and alfentanil. Anesth Analg 1985;64:807–10.
8. Hall RI, Murphy MR, Hug CC. The enflurane sparing effect of sufentanil in dogs. Anesthesiology 1987;67:518–25.
9. Maurer R. Multiplicity of opiate receptors in different species. Neurosci Lett 1982;30:303–7.
10. Robson LE, Gillan MGC, Kosterlitz HW. Species differences in the concentrations and distributions of opioid binding sites. Eur J Pharmacol 1985;112:65–71.
11. Arndt JO, Mikat M, Parasher C. Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. Anesthesiology 1984;61: 355–61.
12. Bailey PL, Port JD, McJames S, Reinersman L, Stanley TH. Is fentanyl an anesthetic in the dog? Anesth Analg 1987;66:542–8.
13. Coulston F, Serrone DM. The comparative approach to the role of nonhuman primates in evaluation of drug toxicity in man: a review. Ann NY Acad Sci 1969;162:681–704.
14. Frost JJ, Wagner HN, Dannals RF, et al. Imaging opiate receptors in the human brain by positron tomography. J Comput Assist Tomogr 1985;9:231–6.
15. Port JD, Stanley TH, Steffey EP, Pace NL, Henrickson R, McJames SW. Intravenous carfentanil in the dog and rhesus monkey. Anesthesiology 1984;61:A378.
16. Golub MS, Anderson JH. Adaptation of pregnant rhesus monkeys to short-term chair restraint. Lab Animal Sci 1986;36: 507–11.
17. Bailey PL, Wilbrink J, Zwanikken P, Pace NZ, Stanley TH. Anesthetic induction with fentanyl. Anesth Analg 1985;64:48–53.
18. Bailey PL, Port JD, Pace NL, Stanley TH, Kimball J. The ED_{50} of carfentanil for elk immobilization with and without the tranquilizer R52703. J Wildlife Manage 1985;49:931–4.
19. McClain DA, Hug CC Jr. Intravenous fentanyl kinetics. Clin Pharmacol Ther 1980;28:106–14.
20. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 1978;57:411–6.
21. Lunn JK, Webster LR, Stanley TH, Woodward A. High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentration and influence of nitrous oxide on cardiovascular responses. Anesth Analg 1979;58:390–5.
22. Wynands JE, Wong P, Townsend GE, Sprigge JS, Whalley DG. Narcotic requirements for intravenous anesthesia. Anesth Analg 1984;63:101–5.
23. Andrews CJH, Sinclair M, Prys-Roberts C, Dye AA. Ventilatory effects during and after continuous infusion of fentanyl or alfentanil. Br J Anaesth 1983;55:211S–6S.
24. Jaffe TB, Ramsey FM. Attenuation of fentanyl-induced truncal rigidity. Anesthesiology 1983;58:562–4.
25. Bourne GH. Collected anatomical and physiological data from the rhesus monkey. In: Bourne GH, ed. The rhesus monkey. Volume I. New York: Academic, 1975:1–63.
26. Wang SC, Glaviano VV. Locus of emetic action of morphine and hydergine in dogs. J Pharmacol Exp Ther 1954;11:329.
27. Harper MH, Hickey RF, Cromwell TH, Linwood S. The magnitude and duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man. J Pharmacol Exp Ther 1976;199:464–8.
28. Rao TLK, Mummanemi N, El-Etr AA. Convulsions: an unusual response to intravenous fentanyl administration. Anesth Analg 1982;61:1020–1.
29. Benthuysen JL, Kien ND, Quam DD. Intracranial pressure during alfentanil-induced rigidity. Anesthesiology 1988;68: 438–40.

Myocardial and Systemic Hemodynamics During Isovolemic Hemodilution Alone and Combined With Nitroprusside-Induced Controlled Hypotension

George J. Crystal, PhD, and M. Ramez Salem, MD

CRYSTAL GJ, SALEM MR. Myocardial and systemic hemodynamics during isovolemic hemodilution alone and combined with nitroprusside-induced controlled hypotension. Anesth Analg 1991;72:227–37.

Myocardial and systemic effects of isovolemic hemodilution alone and combined with controlled hypotension induced with sodium nitroprusside (SNP) were studied in halothane-anesthetized, open-chest dogs. Regional blood flow was measured with radioactive microspheres and used to compute regional oxygen (O_2) supply. Values for regional blood flow in myocardium were used to compute myocardial O_2 (MV_{O_2}) and lactate uptake (MVLAC) using the Fick equation. Hemodilution to hematocrit 50% of baseline increased aortic blood flow and decreased systemic vascular resistance, although other systemic hemodynamic values were not changed. Twofold increases in myocardial blood flow were accompanied by no change in MV_{O_2}, MVLAC, or coronary sinus P_{O_2}. Hemodilution increased regional blood flow sufficiently in the pancreas, liver, duodenum, skeletal muscle, skin, and brain to preserve O_2 supply, whereas unchanged blood flow in the spleen and kidney reduced O_2 supply. Under hemodilution, 15 min of intravenous SNP sufficient to reduce mean arterial pressure by 50% caused parallel reductions in aortic blood flow, dP/dt max, and left ventricular end-diastolic pressure; systemic vascular resistance was unaffected. Myocardial blood flow and MV_{O_2} decreased proportionally, whereas MVLAC and coronary sinus P_{O_2} did not change. Regional blood flow and O_2 supply decreased in the kidney, spleen, liver, and skin. Extending SNP infusion to 60 min increased myocardial blood flow and MV_{O_2}, but other hemodynamic values were unchanged. Comparing previous results with adenosine-induced hypotension inferred that coronary vasodilator reserve was greatly reduced at this time. In conclusion, although myocardial O_2 supply versus demand balance was well maintained during SNP-induced hypotension under hemodiluted conditions, diminished coronary vasodilator reserve suggests increased vulnerability to ischemia if stresses of augmented cardiac work demand or impaired arterial oxygenation were superimposed. The decrease in O_2 supply in the kidney during combined hemodilution and SNP-induced hypotension also warrants concern. These latter findings suggest the need for extensive clinical monitoring when SNP is used for controlled hypotension under hemodiluted conditions.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE. HEART, MYOCARDIAL OXYGENATION. BLOOD, HEMODILUTION.

Anesthesiologists and surgeons are confronted with increasing numbers of hemodiluted patients in the perioperative period. Autologous preoperative blood donation, acute isovolemic hemodilution, preoperative anemia, and use of blood substitutes because of fear of AIDS transmission from donor blood transfusions are among factors contributing to reduced hematocrits in surgical patients (1). Acute isovolemic hemodilution is used increasingly in combination with drug-induced controlled hypotension as a method of blood conservation (2).

Sodium nitroprusside (SNP) is often used to induce controlled hypotension during general anesthesia and to reduce left ventricular afterload and the myocardial work requirement during operation and after myocardial infarction and cardiac failure (3). Myocardial and regional hemodynamic responses during SNP-induced hypotension have been examined extensively in animals with normal hematocrits (4–9). However, recent reports from this laboratory

---

Presented in part at the 11th Annual Meeting of the Society of Cardiovascular Anesthesiologists, April 16–19, 1989, Seattle, Washington and at the 73rd Annual Meeting of the Federation of American Societies for Experimental Biology, March 19–24, 1989, New Orleans, Louisiana.

Received from the Department of Anesthesiology, Illinois Masonic Medical Center; and the Departments of Anesthesiology and Physiology and Biophysics, University of Illinois College of Medicine, Chicago, Illinois. Accepted for publication October 8, 1990.

Address correspondence to Dr. Crystal, Department of Anesthesiology, Illinois Masonic Medical Center, 836 West Wellington Avenue, Chicago, Illinois 60657.

©1991 by the International Anesthesia Research Society

indicating altered vascular responsiveness during hemodilution (10,11) question the applicability of the previous findings to hemodiluted conditions.

The objective of the present study was to evaluate myocardial and systemic hemodynamic responses during isovolemic hemodilution alone and when combined with SNP-induced hypotension in halothane-anesthetized dogs.

Methods

Experimental Preparation

The protocols in this study were approved by the authors' institutional animal investigation committee.

Experiments were performed on mongrel, heartworm-free, conditioned dogs of either sex (weight range, 21.8–24.1 kg). Anesthesia was intravenously induced with 30 mg/kg thiopental sodium. After tracheal intubation, anesthesia was maintained with 0.9% halothane in oxygen, which approximates the 1 MAC dose in the dog (12). Muscle paralysis was obtained with an intravenous injection of 0.1 mg/kg vecuronium bromide, with supplements at 0.05 $mg \cdot kg^{-1} \cdot h^{-1}$. Tidal volume and respiratory rate were initially established to yield physiologic values for $Paco_2$ (Table 1). Once established, ventilatory values were not changed during the course of an experiment. The partial pressure of oxygen, Pco_2, and pH of arterial blood samples were measured electrometrically (model 413, Instrumentation Laboratories, Lexington, Mass.). The hematocrit of blood samples was measured using a microcentrifuge. The rectal temperature was monitored and maintained at 38°C with a heating pad.

Polyethylene cannulas were inserted into (a) the thoracic aorta through the left femoral and right brachial arteries for monitoring aortic blood pressure and for obtaining samples of arterial blood for analysis of gas composition, (b) the right femoral vein for intravenous injections and infusions, and (c) the left femoral vein and right carotid artery for isovolemic exchange of whole blood with dextran solution. The heart was exposed through a left thoracotomy in the fourth intercostal space. A polyethylene cannula was inserted into the left atrium through the left atrial appendage for injecting radioactive microspheres. A micromanometer-tip pressure transducer (Millar Instruments, Houston, Tex.) was inserted into the left ventricle through the left atrium and the mitral valve to measure left ventricular pressure. The left ventricular pressure pulse was differentiated electronically to yield dP/dt max and was used to drive a cardiotachometer. A noncannulating electromagnetic flow transducer was placed around the ascending aorta to measure cardiac output (less coronary blood flow) using an electromagnetic flowmeter (Narco Biosystems, Houston, Tex.). The standard limb lead II of the electrocardiogram was monitored. Heparin (400 U/kg IV) was administered postsurgically to prevent blood coagulation.

Aortic pressure was measured with a Statham transducer (model P23ID, Gould, Cleveland, Ohio) and was averaged electronically. A permanent record of monitored hemodynamic values was obtained with a Gould recorder (model 2800S). Systemic vascular resistance was computed by dividing mean aortic pressure by mean aortic blood flow.

Experimental Measurements

Regional blood flow (RBF) was measured using 15-μm radioactive microspheres as described in detail previously (13–15). Briefly, approximately 1×10^6 microspheres were injected into the left atrium. Simultaneous with each microsphere injection, duplicate reference blood samples were collected at a rate of 6 mL/min for 3 min by using two cannulas of different lengths inserted into the aorta through the right femoral artery. Radioactivity of the duplicate reference samples differed by less than 10%, indicating adequate mixing of the microspheres in the left ventricular output. Autologous blood was simultaneously infused into the dog at the same rate as the reference sample withdrawal to maintain isovolemic conditions. Autologous blood was also used to replace blood samples collected for assessment of myocardial oxygen metabolism.

After the final injection of microspheres, the heart was stopped by intravenous injection of potassium chloride, and tissue samples were excised from the various body organs. Each sample was transferred to a tared counting tube. The tissue and reference blood samples were weighed and analyzed for radioactivity with a gamma scintillation counter equipped with a multichannel analyzer (model 1282-002, LKB, Turku, Finland). Isotope separation was accomplished by standard techniques of gamma spectroscopy. Values for RBF (in $mL \cdot min^{-1} \cdot 100\ g^{-1}$) were calculated from the equation

$$RBF = ABF \times (MC/AC) \times 100,$$

where ABF is the rate of arterial reference sampling (mL/min), MC is microsphere radioactivity ($counts \cdot min^{-1} \cdot g^{-1}$) in the tissue samples, and AC is the total microsphere radioactivity (counts/min) in the arterial reference samples.

Myocardial oxygen consumption. A polyethylene cannula was positioned in the coronary sinus through the right jugular vein and the right atrium for collecting samples of venous effluent from the perfusion field of the left coronary artery. One-milliliter blood samples were simultaneously collected anaerobically from the aorta and the coronary sinus to determine the left coronary arteriovenous oxygen difference. Hemoglobin concentration and percent hemoglobin saturation of blood samples were measured with a CO-oximeter (model 482) and used to calculate oxygen bound to hemoglobin, assuming an oxygen carrying capacity of 1.39 mL $O_2 \cdot 100$ mL $\text{blood}^{-1} \cdot \text{mm Hg}^{-1}$ for hemoglobin (16). The oxygen dissolved in the blood was computed (O_2 dissolved = 0.003 mL $O_2 \cdot 100$ mL $\text{blood}^{-1} \cdot \text{mm Hg}^{-1}$) and added to the bound component to compute total oxygen content.

Myocardial oxygen uptake (MVo_2) (in $\text{mL} \cdot \text{min}^{-1} \cdot 100\ \text{g}^{-1}$) was calculated from the Fick equation:

$$MVo_2 = MBF \times [(a - v)O_2 \text{ difference}/100],$$

where MBF is the arithmetic mean myocardial blood flow for the left ventricular and septal samples in each heart ($\text{mL} \cdot \text{min}^{-1} \cdot 100\ \text{g}^{-1}$) and $(a-v)O_2$ difference is the coronary arteriovenous oxygen difference (vol %).

Convective oxygen supply to the myocardium, as well as to the other regional beds, was computed by multiplying the values for arterial oxygen content and the respective regional blood flow. Systemic oxygen supply was computed by multiplying the values for arterial oxygen content and mean aortic blood flow.

Paired 1-mL blood samples were obtained from the aorta and the coronary sinus and were analyzed for plasma lactate concentration using an enzymatic method (Paramax Analytical System, Baxter, Irvine, Calif.). Myocardial lactate uptake was calculated by substituting the coronary arteriovenous difference for plasma lactate concentration and the plasma flow (determined from the blood flow and hematocrit) into the Fick equation.

Experimental Protocol

The dogs were permitted to stabilize for at least 30 min after surgical preparation before baseline hemodynamic measurements were obtained. Then isovolemic hemodilution was produced by removing blood from the carotid artery at a rate of 20 mL/min while replacing it with 5% dextran (molecular weight 40,000; American McGaw) pumped into the left femoral vein at the same rate. The total volume exchanged was 45 mL/kg, which reduced hematocrit by approximately one-half. The duration of the exchange was 50–54 min. A second set of hemodynamic measurements was obtained after the preparation was permitted to stabilize for 15 minutes after completion of fluid exchange. While in a hemodiluted condition, the dogs then received SNP (Nipride, Roche Products Limited) through a Harvard variable-rate syringe pump at a rate sufficient to reduce mean aortic blood pressure to 50% of baseline. The concentration of the SNP solution was 200 μg/mL (50 mg in 250 mL of 5% dextrose in water). The syringe from which the SNP solution was infused was wrapped in aluminum foil to avoid photodegradation during the experiment (17). After 15 min in the desired state of combined hemodilution and hypotension, a third set of hemodynamic measurements was obtained. The hypotensive infusion of SNP was continued at the same rate for an additional 45 min, at which time another set of hemodynamic measurements was obtained. At that time, the infusion of SNP was stopped, and 30 min was allowed for recovery before final measurements of hemodynamic values were obtained.

Statistical Analysis

A randomized block analysis of variance in conjunction with the Student-Newman-Keuls test was used to assess significance of differences among experimental conditions (Tables 1–5; Figure 2) (18). For results in Figure 2, the Student's *t*-test for paired samples (18) was also used to assess significance of differences from control values for regional oxygen supply. A $P < 0.05$ was considered statistically significant throughout this study.

Results

Systemic Data

Systemic data are presented in Tables 1 and 2. Hemodilution caused an approximate 50% reduction in hematocrit and hemoglobin concentration resulting in proportional reductions in arterial oxygen content. Arterial pH and Po_2 decreased modestly, whereas arterial Pco_2 and lactate concentration were not affected. Hemodilution reduced systemic vascular resistance but did not change mean aortic pressure. Increases in aortic blood flow blunted the decreases in systemic oxygen supply caused by the reductions in arterial oxygen content. These increases in aortic blood flow resulted from increases in stroke volume as heart rate did not change. Hemodilution alone had

Table 1. Arterial Blood Values During Isovolemic Hemodilution Alone and Combined With 15 and 60 Min of Sodium Nitroprusside-Induced Hypotension

	Control	HD alone	HD-HYPO (15 min)	HD-HYPO (60 min)	Recovery
Po_2	327 ± 29	277 ± 36^a	196 ± $25^{a,b}$	161 ± $27^{a,b}$	205 ± $27^{a,b}$
Pco_2	38 ± 1	40 ± 2	40 ± 3	45 ± $2^{a,b,c}$	45 ± $3^{a,b,c}$
pH	7.40 ± 0.01	7.34 ± 0.02^a	7.30 ± 0.02^a	7.26 ± $0.03^{a,b,c}$	7.27 ± $0.04^{a,b,c}$
So_2	95.8 ± 1.0	96.6 ± 0.8	95.4 ± 1.0	93.8 ± 1.5	94.1 ± 1.7
HCT	42 ± 2	23 ± 1^a	22 ± 2^a	24 ± 2^a	24 ± 2^a
Co_2	20.5 ± 1.3	11.7 ± 0.6^a	11.3 ± 0.7^a	11.0 ± 0.7^a	11.3 ± 0.8^a
HG	14.8 ± 0.6	8.1 ± 0.4^a	7.8 ± 0.5^a	8.2 ± 0.5^a	8.1 ± 0.5^a
LAC	2.7 ± 0.4	2.6 ± 0.4	3.0 ± 0.4	3.3 ± 0.4	3.3 ± 0.4

HD, hemodilution; HYPO, hypotension; Po_2, oxygen tension (mm Hg); Pco_2, carbon dioxide tension (mm Hg); So_2, oxygen saturation of hemoglobin (%); HCT, hematocrit (%); Co_2, oxygen content (vol %); HG, hemoglobin concentration (g/100 mL); LAC, plasma lactate concentration (mEq/L).

Values are mean ± SE for nine dogs.

[a] $P < 0.05$, from control.

[b] $P < 0.05$, from HD alone.

[c] $P < 0.05$, from HD-HYPO (15 min).

Table 2. Systemic Hemodynamic Values During Isovolemic Hemodilution Alone and Combined With 15 and 60 Min of Sodium Nitroprusside-Induced Hypotension

	Control	HD alone	HD-HYPO (15 min)	HD-HYPO (60 min)	Recovery
MAP	99 ± 7	91 ± 6	45 ± $2^{a,b}$	51 ± $5^{a,b}$	78 ± $6^{a,b,c,d}$
SAP	116 ± 8	115 ± 6	59 ± $4^{a,b}$	64 ± $6^{a,b}$	96 ± $6^{a,b,c,d}$
DAP	87 ± 6	78 ± 6^a	37 ± $2^{a,b}$	41 ± $4^{a,b}$	67 ± $6^{a,b,c,d}$
HR	132 ± 8	143 ± 6	142 ± 7	151 ± 9^a	148 ± 8^a
AOF	1741 ± 170	2539 ± 241^a	1619 ± 118^b	1565 ± 112^b	1571 ± 123^b
SV	13.8 ± 1.8	17.9 ± 1.8^a	11.7 ± $1.1^{a,b}$	10.6 ± $0.9^{a,b}$	10.8 ± $1.0^{a,b}$
SVR	0.06 ± 0.01	0.04 ± 0.01^a	0.03 ± 0.01^a	0.03 ± 0.01^a	0.05 ± $0.01^{a,b,c,d}$
So_2S	355 ± 36	305 ± 40^a	180 ± $21^{a,b}$	178 ± $19^{a,b}$	182 ± $23^{a,b}$
dP/dt max	744 ± 66	778 ± 57	439 ± $39^{a,b}$	549 ± $60^{a,b,c}$	572 ± $49^{a,b,c}$
LVEDP	4.6 ± 0.5	4.9 ± 0.5	2.6 ± $0.4^{a,b}$	2.1 ± $0.4^{a,b}$	4.0 ± $0.4^{c,d}$

HD, hemodilution; HYPO, hypotension; MAP, mean aortic pressure (mm Hg); SAP, systolic aortic pressure (mm Hg); DAP, diastolic aortic pressure (mm Hg); HR, heart rate (beats/min); AOF, aortic blood flow (mL/min); SV, stroke volume (mL): SVR, systemic vascular resistance (mm Hg·mL^{-1}·min^{-1}); So_2S systemic oxygen supply (mL/min); dP/dt max, maximum rate of change of left ventricular systolic pressure (mm Hg/s); LVEDP, left ventricular end-diastolic pressure (mm Hg).

Values are mean ± SE for nine dogs.

[a] $P < 0.05$, from control.

[b] $P < 0.05$, from HD alone.

[c] $P < 0.05$, from HD-HYPO (15 min).

[d] $P < 0.05$, from HD-HYPO (60 min).

no effect on left ventricular dP/dt max or on end-diastolic pressure.

The average dose of SNP required to reduce mean aortic pressure by one-half after hemodilution was 7.3 ± 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which corresponded to an infusion rate of SNP solution of 0.83 ± 0.09 mL/min. The total amount of SNP infused during the 60 min of hypotension averaged 438 ± 47 μg/kg.

Figure 1 presents a representative tracing demonstrating initial changes in monitored hemodynamic values during a hypotensive infusion of SNP under hemodiluted conditions. The induced decrease in mean aortic pressure was accompanied by parallel decreases in aortic blood flow, left ventricular dP/dt max, and left ventricular end-diastolic pressure. Heart rate increased only modestly and the electrocardiogram remained normal.

The initial hemodynamic responses to SNP-induced hypotension under hemodiluted conditions (Figure 1) were maintained during the course of the hypotensive period, as is evident from the mean values summarized in Table 1. At 15 min of SNP infusion, mean aortic blood pressure and aortic blood flow were decreased proportionally, implying no change in systemic vascular resistance. As arterial oxygen content did not change, systemic oxygen supply was reduced in proportion to the decrease in aortic blood flow. Left ventricular dP/dt max and end-diastolic pressure remained decreased at 15 min of SNP infusion and heart rate was unchanged.

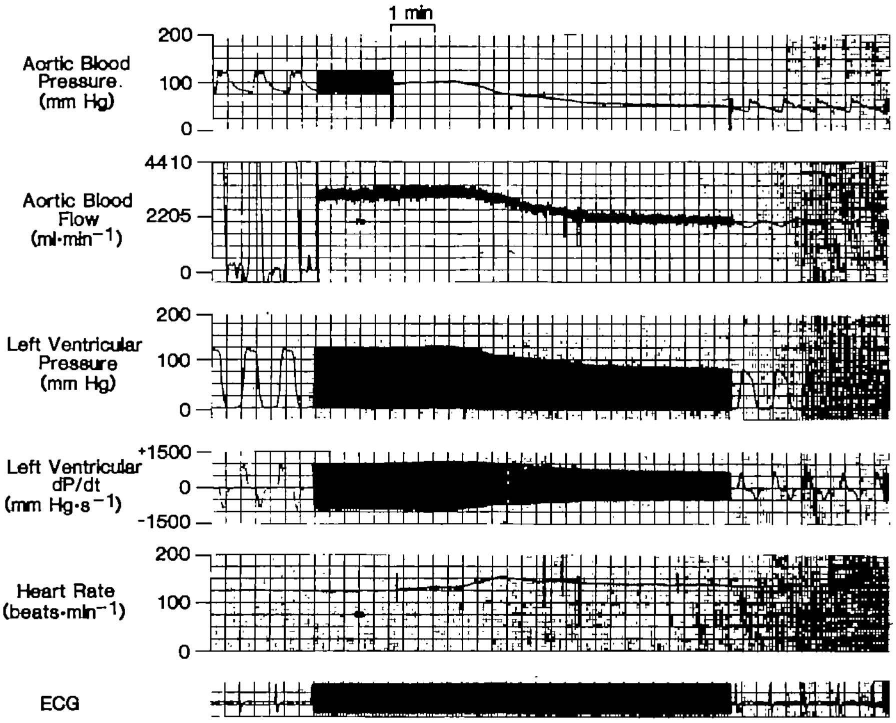


Figure 1. Representative tracing demonstrating initial changes in monitored hemodynamic values during an intravenous hypotensive infusion of SNP in hemodiluted dog. The decrease in mean aortic pressure was accompanied by parallel decreases in aortic blood flow, left ventricular dP/dt max, and left ventricular end-diastolic pressure (ECG, electrocardiogram.)

Arterial blood values did not change from the values evident during hemodilution alone with the exception of Po_2, which decreased.

Extending the SNP infusion without change in rate to 60 min was associated with no further changes in systemic hemodynamic values, although arterial pH decreased and Pco_2 increased. Noteworthy was the lack of recovery of aortic pressure indicative of tachyphylaxis to SNP.

Aortic and left ventricular end-diastolic pressures returned toward baseline after discontinuation of SNP infusion, whereas aortic blood flow and left ventricular dP/dt max remained reduced. There was no evidence of rebound hypertension. The decreases in arterial Po_2 and increases in arterial Pco_2 persisted.

Myocardial Data

Myocardial data are presented in Tables 3 and 4. Hemodilution alone caused increases in myocardial blood flow in the left and right ventricular free walls and interventricular septum. These increases in blood flow were essentially transmurally uniform and were sufficient to maintain regional oxygen supply at the control level. Hemodilution alone had no effect on myocardial oxygen uptake because the increases in myocardial blood flow were sufficient to offset reductions in the coronary arteriovenous oxygen content difference. Neither coronary sinus Po_2 nor myocardial lactate uptake was affected by hemodilution alone.

Fifteen minutes of SNP-induced hypotension reduced myocardial blood flow transmurally in all regions of the heart relative to the values evident during hemodilution alone. However, these decreases did not reach statistical significance in the right ventricular free wall. Myocardial oxygen supply and oxygen uptake decreased proportionally, resulting in no change in the coronary arteriovenous oxygen content difference or in coronary sinus Po_2 from the values evident during hemodilution alone. Fifteen minutes of SNP infusion during hemodilution had no effect on myocardial lactate uptake.

Extending SNP infusion to 60 min increased myocardial blood flow in all regions of the heart from values evident after 15 min of infusion. Myocardial oxygen uptake increased to a value not significantly different from that during hemodilution alone. The increase in myocardial oxygen uptake was less than proportional to the increase in myocardial blood flow, resulting in reductions in the coronary arteriovenous oxygen difference and in increases in coronary sinus Po_2. The percentage of lactate extraction decreased, but myocardial lactate uptake was well preserved. The electrocardiogram remained normal throughout the hemodilution-hypotension protocol. After cessation of SNP infusion, myocardial variables returned to values similar to those during hemodilution alone.

Table 3. Regional and Mean Transmural Myocardial Blood Flow During Isovolemic Hemodilution Alone and Combined With Sodium Nitroprusside-Induced Hypotension

	Control	HD alone	HD-HYPO (15 min)	HD-HYPO (60 min)	Recovery
Left ventricle					
Epicardium	63 ± 8	130 ± 15[a]	101 ± 7[a,b]	143 ± 10[a,c]	127 ± 13[a,c]
Midmural	61 ± 8	125 ± 17[a]	94 ± 7[a,b]	127 ± 14[a,c]	119 ± 15[a,c]
Endocardium	63 ± 8	122 ± 17[a]	77 ± 7[b]	108 ± 17[a,c]	111 ± 13[a,c]
Mean	62 ± 8	126 ± 16[a]	91 ± 5[a,b]	126 ± 13[a,c]	119 ± 15[a,c]
Endo/epi	1.1 ± 0.1	0.9 ± 0.1[a]	0.9 ± 0.1[a]	0.9 ± 0.1[a]	0.9 ± 0.1[a]
Right ventricle					
Epicardium	46 ± 8	92 ± 10[a]	78 ± 4[a]	112 ± 7[a,c]	93 ± 11[a]
Endocardium	52 ± 8	94 ± 13[a]	83 ± 5[a]	121 ± 11[a,b,c]	93 ± 12[a,d]
Mean	49 ± 8	93 ± 11[a]	80 ± 4[a]	116 ± 9[a,b,c]	93 ± 11[a,d]
Endo/epi	1.1 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
Septum					
Right ventricle	59 ± 11	114 ± 18[a]	99 ± 7[a]	133 ± 14[a,c]	113 ± 14[a]
Midmural	67 ± 13	126 ± 20[a]	97 ± 9[a,b]	133 ± 18[a,c]	120 ± 16[a,c]
Left ventricle	65 ± 10	128 ± 22[a]	81 ± 11[b]	104 ± 16[a]	118 ± 19[a,c]
Mean	64 ± 11	123 ± 20[a]	92 ± 8[a,b]	122 ± 16[a,c]	116 ± 16[a,c]
LV/RV	1.2 ± 0.1	1.1 ± 0.1	0.8 ± 0.1[a,b]	0.8 ± 0.1[a,b]	1.0 ± 0.1[c,d]

HD, hemodilution; HYPO, hypotension; Endo/epi, endocardium/epicardium; LV, left ventricle; RV, right ventricle.

Values are mean ± SE in nine dogs; blood flows, in mL·min^{-1}·100 g^{-1}.

[a] $P < 0.05$, from control.

[b] $P < 0.05$, from HD alone.

[c] $P < 0.05$, from HD-HYPO (15 min).

[d] $P < 0.05$, from HD-HYPO (60 min).

Table 4. Myocardial Oxygen Consumption and Related Values During Isovolemic Hemodilution Alone and Combined With 15 and 60 Min of Sodium Nitroprusside-Induced Hypotension

	Control	HD alone	HD-HYPO (15 min)	HD-HYPO (60 min)	Recovery
MVo$_2$	7.8 ± 1.0	8.4 ± 0.8	5.5 ± 0.3[a,b]	6.8 ± 0.8	7.7 ± 0.9[c]
MBF	63 ± 9	124 ± 18[a]	91 ± 7[a,b]	124 ± 14[a,c]	118 ± 15[a,c]
(a−v)O$_2$ diff	12.6 ± 0.6	7.2 ± 0.5[a]	6.1 ± 0.3[a]	5.5 ± 0.5[a,b]	6.6 ± 0.4[a]
O$_2$ extraction	62 ± 2	61 ± 3	56 ± 2	51 ± 6	60 ± 3
O$_2$ supply	13.0 ± 2.1	14.0 ± 1.5	9.7 ± 3.9[a]	13.7 ± 1.5[c]	12.8 ± 1.5[c]
MVLAC	58 ± 16	83 ± 9	60 ± 7	51 ± 14	54 ± 10
LAC extraction	56 ± 2	39 ± 4[a]	31 ± 3[a]	16 ± 5[a,b,c]	21 ± 4[a,b,c]
Coronary sinus blood values					
Po$_2$	30 ± 1	32 ± 1	34 ± 2[a]	40 ± 2[a,b,c]	36 ± 2[a,b]
Pco$_2$	48 ± 2	49 ± 2	50 ± 2	51 ± 2	52 ± 3
pH	7.35 ± 0.01	7.28 ± 0.01[a]	7.27 ± 0.02[a]	7.24 ± 0.03[a]	7.25 ± 0.03[a]
So$_2$	38 ± 3	38 ± 3	42 ± 3	49 ± 4	41 ± 2
Co$_2$	7.8 ± 0.6	4.5 ± 0.4[a]	4.9 ± 0.5[a]	5.6 ± 0.8[a]	4.6 ± 0.6[a]
LAC	1.3 ± 0.3	1.6 ± 0.4	2.1 ± 0.4[a]	2.7 ± 0.3[a,b]	2.7 ± 0.4[a,b]

HD, hemodilution; HYPO; hypotension; MVo$_2$, myocardial oxygen uptake (mL·min^{-1}·100 g^{-1}); MBF, myocardial blood flow (mL·min^{-1}·100 g^{-1}); (a−v)O$_2$ diff, left coronary arteriovenous oxygen content difference (vol %); O$_2$ extraction, myocardial oxygen extraction (%); O$_2$ supply, myocardial oxygen supply (mL·min^{-1}·100 g^{-1}); MVLAC, myocardial lactate uptake (μEq·min^{-1}·100 g^{-1}); LAC extraction, myocardial lactate extraction (%), Po$_2$, partial pressure of oxygen; Pco$_2$, partial pressure of carbon dioxide; So$_2$, oxygen saturation of hemoglobin (%).

Values are mean ± SE in nine dogs.

[a] $P < 0.05$, from control.

[b] $P < 0.05$, from HD alone.

[c] $P < 0.05$, from HD-HYPO (15 min).

Regional Data

Regional data are presented in Table 5 and Figure 2. Hemodilution alone increased blood flow in the pancreas, liver (hepatic circulation), and skin, thus maintaining regional oxygen supply. Although no statistically significant change in blood flow was evident in the duodenum and the skeletal muscle, the tendency for increased flow in these tissues was sufficient to maintain regional oxygen supply. Hemodilution alone had no effect on blood flow in renal

Table 5. Regional Blood Flows During Isovolemic Hemodilution Alone and Combined With 15 and 60 Min of Sodium Nitroprusside-Induced Hypotension

	Control	HD alone	HD-HYPO (15 min)	HD-HYPO (60 min)	Recovery
Renal cortex	515 ± 56	617 ± 51	291 ± 40^{a,b}	218 ± 42^{a,b}	436 ± 64^{b,c,d}
Spleen	192 ± 25	223 ± 43	79 ± 11^{a,b}	79 ± 16^{a,b}	163 ± 32^{c,d}
Duodenum	36 ± 5	51 ± 5	72 ± 8^{a}	86 ± 8^{a,b}	67 ± 8^{a}
Pancreas	12 ± 1	25 ± 3^{a}	26 ± 2^{a}	28 ± 3^{a}	28 ± 3^{a}
Liver	27 ± 5	50 ± 10^{a}	28 ± 5^{b}	27 ± 3^{b}	38 ± 3^{b}
Skin	2.7 ± 0.2	4.2 ± 0.5^{a}	2.3 ± 0.2^{b}	2.8 ± 0.2^{b}	3.4 ± 0.5^{b}
Skeletal muscle	3.4 ± 0.8	5.1 ± 1.6	3.9 ± 0.5	3.9 ± 0.4	4.8 ± 0.8
Brain					
Cerebral cortex	52 ± 4	67 ± 6	61 ± 7	68 ± 8	76 ± 5^{a}
Cerebellum	42 ± 1	55 ± 4^{a}	51 ± 4^{a}	55 ± 4^{a}	66 ± 6^{a,c}
Pons	30 ± 2	40 ± 6	42 ± 6	46 ± 7^{a}	50 ± 7^{a}
Medulla	25 ± 4	33 ± 4	34 ± 3	37 ± 4^{a}	37 ± 5^{a}
Spinal cord	19 ± 3	27 ± 4^{a}	26 ± 4^{a}	28 ± 5^{a}	29 ± 5^{a}

Values are mean ± SE in nine dogs; blood flows, in mL·min^{-1}·100 g^{-1}.
[a] $P < 0.05$, from control.
[b] $P < 0.05$, from HD alone.
[c] $P < 0.05$, from HD-HYPO (15 min).
[d] $P < 0.05$, from HD-HYPO (60 min).

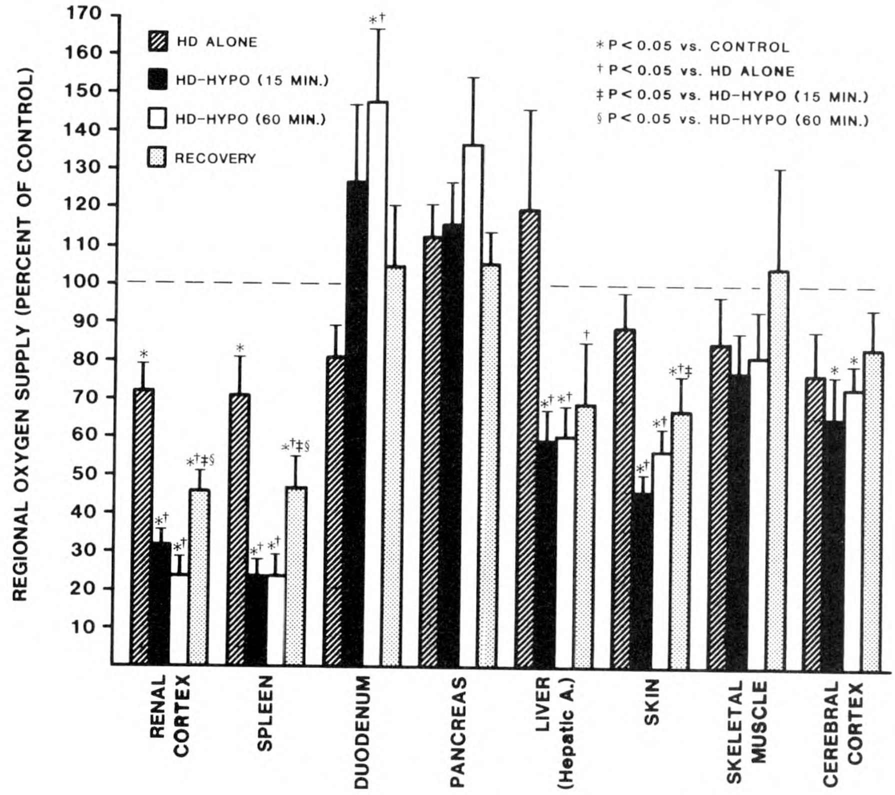


Figure 2. Effect of hemodilution (HD) alone and combined with SNP-induced hypotension (HD-HYPO) on regional oxygen supply.

cortex and spleen, but in the presence of reduced arterial oxygen content it decreased regional oxygen supply.

Hemodilution alone caused increases in blood flow in all regions of the brain, but statistical significance was achieved only in the cerebellum and the spinal cord. These increases in blood flow were adequate to offset the decreases in arterial oxygen content and to maintain regional oxygen supply.

Fifteen minutes of SNP-induced hypotension reduced blood flow and oxygen supply in the renal cortex, spleen, liver, and skin from values evident during hemodilution alone but had no effects on these variables in the duodenum, pancreas, and skeletal muscle. Blood flow and oxygen supply in the cerebral cortex were decreased modestly.

Sodium nitroprusside-induced changes in blood flow and oxygen supply in peripheral beds were essentially stable during the 60-min duration of infusion.

After discontinuation of SNP infusion, values for regional blood flow and oxygen supply returned toward values during hemodilution alone, although modest reductions in these variables persisted in the renal cortex, spleen, liver, and skin.

Discussion

Effects of Isovolemic Hemodilution Alone

Because the systemic and regional hemodynamic effects of isovolemic hemodilution alone have been described in detail in previous reports from this laboratory (13–15), they will be dealt with only briefly here. Hemodilution was associated with increased cardiac output secondary to increased stroke volume. Such increased stroke volume has been attributed to the combined effects of augmented myocardial contractility owing to activation of the cardiac sympathetic nerves (19) and to decreased impedance to left ventricular ejection because of reduced blood viscosity and peripheral vasodilation (15).

Inasmuch as coronary perfusion pressure (aortic pressure) was essentially constant, the increases in myocardial blood flow were secondary to decreased vascular resistance. Although reduced blood viscosity presumably contributed to the decreased vascular resistance, the constancy of coronary sinus P_{O_2} suggests fine-tuning by a metabolic vasodilator mechanism (20). Undiminished myocardial lactate uptake during hemodilution is consistent with well-maintained myocardial oxygen supply/demand balance (21).

In the absence of samples of local venous effluent and of metabolic data, it is impossible to evaluate conclusively whether delivery of oxygen to cerebral tissue remained adequate during hemodilution. However, several observations suggest that this was the case. First, convective oxygen supply was maintained throughout the brain and spinal cord. Second, regional cerebral blood flow remained constant during the subsequent period of induced hypotension, suggesting that a vasodilator reserve was available. It seems reasonable to assume that this reserve would have been recruited by local metabolic mechanisms, if necessary, to maintain adequate cerebral oxygenation during hemodilution alone. Third, previous studies demonstrated unimpaired electroencephalographic activity and lack of anaerobic metabolism during comparable isovolemic hemodilution in anesthetized dogs (22,23).

Blood flow in several peripheral tissues, e.g., renal cortex, was unchanged during hemodilution resulting in reduced oxygen supply. This suggests that localized vasoconstriction in these tissues negated the facilitatory influence of reduced viscosity on blood flow. Although our data provide no information on the mechanism(s) responsible for this vasoconstriction, a role for the sympathetic vasoconstrictor nerves has been suggested (13). Whether reduced oxygen supply limited metabolism and/or function in individual peripheral tissues cannot be assessed from the available data. However, the lack of increase in arterial plasma lactate concentration implies absence of anaerobic metabolism on a systemic basis and satisfaction of whole body oxygen requirements.

Effects of Sodium Nitroprusside Hypotension During Isovolemic Hemodilution

Previous studies have demonstrated that SNP has the ability to relax both arteriolar and venous smooth muscle (24). In the nonhemodiluted dogs of previous studies, SNP caused hypotension by a decrease in systemic vascular resistance, inferring predominant arteriolar smooth muscle relaxation (5,6,8). In contrast, in the hemodiluted dogs of the present study, SNP caused hypotension by a decrease in cardiac output. This decrease in cardiac output was associated with reduced ventricular filling pressure (as evidenced by reduced left ventricular end-diastolic pressure), suggesting predominant venous smooth muscle relaxation. The mechanism by which hemodilution causes the vascular focus for SNP to shift from the arterial to the venous side of the circulation awaits clarification.

The rate of SNP infusion for the hemodiluted dogs of the present study was significantly less (range, one-half to one-tenth) than that demonstrated previously for comparable hypotension in nonhemodiluted dogs anesthetized with halothane (5,6). The total dose of SNP for the hemodiluted dogs of the present study was well below the dose (1.0 mg/kg) that has been demonstrated to cause the severe metabolic acidosis (arterial pH = 7.18 ± 0.03) characteristic of cyanide toxicity in nonhemodiluted dogs (9). The reduced dose requirement for SNP during hemodilution may reflect the predominant venous mechanism for hypotension under this condition.

Tachyphylaxis and rebound hypertension are two major disadvantages associated with SNP-induced hypotension under nonhemodiluted conditions (5). These effects have been attributed to peripheral vasoconstriction secondary to baroreceptor-mediated activation of the sympathoadrenal and renin-angiotensin systems. Neither tachyphylaxis nor rebound hypertension was evident in the hemodiluted dogs of the present study.

At 15 min of SNP-induced hypotension in hemodiluted dogs, myocardial blood flow (as well as convective oxygen supply) was reduced. This decrease in blood flow was proportional to the decrease in myocardial oxygen uptake, thus apparently reflecting the influence of metabolically linked vascular control mechanisms (20). The constancy of coronary sinus Po_2, arteriovenous oxygen content difference, and lactate uptake during this early stage of hypotension is consistent with well-maintained global myocardial oxygen supply versus demand balance (20,21).

The decrease in myocardial oxygen uptake during the infusion of SNP was likely mainly due to the decrease in left ventricular pressure (in accordance with the law of Laplace, a reflection of wall tension) (25). Although left ventricular dP/dt max decreased, the concomitant reduction in aortic pressure rendered this measurement an unreliable index of global left ventricular myocardial contractility (26).

In contrast to the present findings in hemodiluted dogs, the decrease in myocardial oxygen demand occurring during SNP-induced hypotension in nonhemodiluted dogs was usually associated with either no change or an increase in the rate of myocardial blood flow (4,5). This suggests a direct coronary vasodilating effect of SNP sufficient to override metabolic control of myocardial perfusion (20). The absence of this effect during hemodilution may reflect the reduced rate of SNP infusion required for hypotension. This notion is supported by previous studies in nonhemodiluted dogs demonstrating that the vasodilating effect of SNP in the coronary circulation shows a strong dose dependence (27).

Extending SNP-induced hypotension to 60 min caused increases in myocardial blood flow in all regions of the heart, accompanied by increased myocardial oxygen uptake. As the rate of infusion of SNP was not altered, these responses were likely not related to increased circulating levels of SNP, but rather were related to factors secondary to prolonged infusion of SNP under hemodiluted conditions. Although a portion of the increase in myocardial blood flow was apparently due to metabolically induced vasodilation, the increases in coronary sinus Po_2 and oxyhemoglobin saturation were consistent with a contribution from an extrinsic vasodilator mechanism, perhaps reduced arterial pH (20). Similar delayed increases in myocardial blood flow and oxygen uptake were reported for nonhemodiluted dogs during SNP-induced hypotension and were attributed to the elevated circulating levels of catecholamines observed (5). The maintenance of lactate uptake during prolonged isovolemic hemodilution and during SNP-induced hypotension suggests that on a global basis myocardial oxygen demands were apparently satisfied and no anaerobic metabolism was evident.

The available coronary vasodilator reserve during combined hemodilution and SNP-induced hypotension was not assessed in the present study. However, insight into its magnitude can be obtained by comparing the present myocardial blood flows with those from our previous study in which an intravenous infusion of adenosine, at a rate sufficient to cause maximal coronary vasodilation, was used to induce comparable hypotension in hemodiluted, anesthetized, open-chest dogs (13). This analysis indicates that at 15 min of combined hemodilution and SNP-induced hypotension, a significant flow reserve was evident in all regions of the heart, ranging from 130% in the left ventricular subendocardium to 207% in the right ventricular subepicardium. Although the values for coronary flow reserve were well below the 500%–600% values evident under normal conditions (28), they represent an appreciable vascular capacity available for recruitment. As stated above, prolonged infusion of SNP was accompanied by increases in myocardial blood flow in all regions of the heart (secondary to coronary vasodilation), which, of course, reduced the coronary vasodilator reserve on a global basis. At 60 min of combined hemodilution and SNP-induced hypotension, the region with the lowest flow reserve remained the left ventricular subendocardium, which had a value of 64%. This implies a significantly compromised capability for local vasodilator adjustments in response to augmented cardiac work demands or to impaired arterial oxygenation, and thus an enhanced vulnerability for myocardial ischemia under either of those conditions.

The capability for pressure-flow autoregulation within the brain and the spinal cord is well documented (29). Although previous studies have demonstrated that hemodilution may diminish cerebral vasodilator reserve (23), this reserve remained sufficient in all regions of the brain to maintain blood flow in spite of the induced 50% decrease in perfusion pressure.

Sodium nitroprusside-induced hypotension was associated with decreased blood flow in selected peripheral tissues, the most noteworthy of which was the kidney. The decreases in renal blood flow in the present study were similar to those demonstrated previously during comparable SNP-induced hypotension in anesthetized dogs with normal hematocrit (6), although the reduction in renal oxygen supply was accentuated in the present study because of decreased arterial oxygen content. The observed decrease in renal blood flow was proportional to the decrease in aortic pressure, which indicated lack of pressure-flow autoregulation. Apparently, the tendency for compensatory vasodilation in the renal circulation was nullified by a vasoconstrictor mechanism, e.g., the sympathetic vasoconstrictor nerves acting through the arterial baroreceptors.

The observed decrease in arterial Po_2 during SNP-induced hypotension in the hemodiluted dogs of the present study is in keeping with observations obtained in nonhemodiluted dogs (17). This phenomenon has been attributed to the tendency of SNP to impair hypoxic vasoconstriction in the pulmonary circulation, thus resulting in ventilation/perfusion mismatch. This factor was likely aggravated in the present study by decreased mixed venous O_2, which would be an expected consequence of reduced cardiac output although not verified by actual measurements. Despite the reduction in arterial Po_2, it remained sufficient to maintain relatively complete oxyhemoglobin saturation, resulting in little change in arterial oxygen content.

The lack of increased arterial lactate concentration during the period of combined SNP-induced hypotension and hemodilution suggests that, at least on a systemic level, tissue oxygen demands were satisfied and cyanide toxicity was not present.

In summary, SNP-induced hypotension for as long as 60 min appeared reasonably well tolerated by body tissues during hemodilution under halothane anesthesia, although coronary vasodilator reserve was compromised and oxygen supply to the kidney was reduced.

Clinical Implications

The present findings pertain strictly to the specific conditions of the study and should be extrapolated to human patients only with caution. Results may have varied if another anesthetic with different cardiovascular effects, such as isoflurane (30), or a diluent with a different viscosity or ionic composition, such as saline or plasma (31), were used. Although there is no evidence to our knowledge that human and canine coronary vascular smooth muscle respond qualitatively differently to SNP, quantitative differences in dose-response relations cannot be discounted.

The above caveats notwithstanding, the present findings suggest that the heart and kidneys may be the most vulnerable organs during combined isovolemic hemodilution and SNP-induced hypotension. This suggests the need for extensive clinical monitoring with particular attention to these organs in patients in whom this condition exists.

The authors appreciate the expert technical assistance of Derrick L. Harris, BS.

References

1. Biro GP. Anaemia and hemodilution. In: Prys-Roberts C, ed. The circulation in anaesthesia. Oxford: Blackwell Scientific, 1980:327–50.
2. Fahmy NR. Haemodilution and hypotension. In: Enderby GEH, ed. Hypotensive anaesthesia. Edinburgh: Churchill Livingstone, 1985;164–85.
3. Tinker JH, Michenfelder JD. Sodium nitroprusside. Pharmacology, toxicology, and therapeutics. Anesthesiology 1976;45:340–54.
4. Bagshaw RJ, Cox RH, Campbell KB. Sodium nitroprusside and regional arterial hemodynamics in the dog. Br J Anaesth 1977;49:735–43.
5. Bloor BC, Fukunga AF, Ma C, et al. Myocardial hemodynamics during induced hypotension: a comparison between sodium nitroprusside and adenosine triphosphate. Anesthesiology 1985;63:517–25.
6. Colley PS, Sivarajan M. Regional blood flow in dogs during halothane anesthesia and controlled hypotension produced by nitroprusside or nitroglycerin. Anesth Analg 1984;63:503–10.
7. Kassell NF, Boarini DJ, Sprowell JA, Olin JA. Pharmacologically induced profound arterial hypotension in the anesthetized dog. J Neurosurg 1983;58:77–83.
8. Kien NG, White DA, Reitan JA, Eisele JH Jr. Cardiovascular function during controlled hypotension induced by adenosine triphosphate or sodium nitroprusside in the anesthetized dog. Anesth Analg 1987;66:103–10.
9. Michenfelder JD, Theye RA. Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimethaphan, halothane, or nitroprusside. Anesthesiology 1977;46:188–95.
10. Czinn EA, Crystal GJ, Kang M, Salem MR. Hemodilution abolishes hypocapnia-induced vasoconstrictor responses in brain and spinal cord (abstract). Anesthesiology 1989;71:A606.
11. Mahdi M, Crystal GJ, Salem MR, Paulissian R. Hemodilution attenuates pressor responses during phenylephrine infusions in dogs (abstract). Anesth Analg 1990;70:S254.
12. Eger EI II. Anesthetic uptake and action. Baltimore: Williams & Wilkins, 1974:1–25.
13. Crystal GJ, Rooney MW, Salem MR. Regional hemodynamics and oxygen supply during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. Anesth Analg 1988;67:211–8.
14. Crystal GJ, Rooney MW, Salem MR. Myocardial blood flow and oxygen consumption during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. Anesth Analg 1988;67:539–47.

15. Crystal GJ, Ruiz JR, Rooney MW, Salem MR. Regional hemodynamics and oxygen supply during isovolemic hemodilution in the absence and presence of high-grade β-adrenergic blockade. J Cardiothorac Anesth 1988;2:772–9.
16. Weibel ER. The pathway for oxygen. Cambridge: Harvard University Press, 1984;138–51.
17. Verner IR. Techniques for deliberate hypotension. Direct acting vasodilators. In: Enderby GEH, ed. Hypotensive anesthesia. Edinburgh: Churchill Livingstone, 1985:138–63.
18. Zar JH. Biostatistical analysis. Englewood Cliffs, NJ: Prentice-Hall, 1974.
19. Glick G, Plauth WH Jr, Braunwald E. Role of autonomic nervous system in circulatory response to acutely induced anemia in unanesthetized dog. J Clin Invest 1964;43:2112–4.
20. Feigl EM. Coronary physiology. Physiol Rev 1983;63:1–205.
21. Shea TM, Watson RM, Piotrowski SF, Dermksian G, Case RB. Anaerobic myocardial metabolism. Am J Physiol 1962;203: 463–9.
22. Michenfelder JD, Theye RA. The effects of profound hypocapnia and dilutional anemia on canine cerebral metabolism and blood flow. Anesthesiology 1969;31:449–57.
23. Maruyama M, Shimoj K, Ichikawa T, Hashiba M, Naita E. The effects of extreme hemodilution on the autoregulation of cerebral blood flow, electroencephalogram and cerebral metabolic rate in the dog. Stroke 1984;16:675–79.
24. Miller RR, Vismara LA, Zelis R, Amsterdam EA, Mason DT. Clinical use of sodium nitroprusside in chronic ischemic heart disease. Effects on peripheral vascular resistance and venous tone and on ventricular volume, pump, and mechanical performance. Circulation 1975;51:328–36.
25. Braunwald E. Control of myocardial oxygen consumption. Am J Cardiol 1971;27:416–32.
26. Mason DT. Usefulness and limitations of the rate of rise of intraventricular pressure (dP/dt) in the evaluation of myocardial contractility. Am J Cardiol 1969;23:516–27.
27. Acad B, Sonn J, Furman E, Scheinowitz M, Kedem J. Specific effects of nitroprusside on myocardial O_2 balance following coronary ligation in the dog heart. J Cardiovasc Pharmacol 1987;9:79–86.
28. Crystal GJ, Downey HF, Bashour FA. Small vessel and total coronary blood volume during intracoronary adenosine. Am J Physiol 1981;241:H194–200.
29. Mueller SM, Heistad DD, Marcus ML. Total and regional cerebral blood flow during hypotension, hypertension, and hypocapnia. Effect of sympathetic denervation in dogs. Circ Res 1977;41:350–6.
30. Warren TM, Stoelting RK. Hemodynamic effects of general anesthetics. In: Altura BM, Halevy S, eds. Cardiovascular actions of anesthetics and drugs used in anesthesia. Basel: Karger, 1986;3–50.
31. Tremper KK, Waxman K. Artificial plasma expanders. In: Stoelting RK, Barash PG, Gallagher TJ, eds. Advances in anesthesia. Volume 2. Chicago: Year Book, 1985:293–316.

ANESTH ANALG
1991;72:238–40

Clinical Reports

Is Hypoxic Pulmonary Vasoconstriction Exaggerated During One-Lung Ventilation in Patients With Patent Ductus Arteriosus?

Anis S. Baraka, MD, Samar K. Taha, MD, and Rania A. El-Khatib, MD

Key Words: HEART, CONGENITAL DEFECTS—patent ductus arteriosus. VENTILATION, ONE LUNG—patent ductus arteriosus. ANESTHETIC TECHNIQUES, ENDOBRONCHIAL—pulmonary shunt.

During two-lung ventilation (TLV) in the lateral decubitus position, the nondependent lung receives approximately 40% of the total blood flow (1), and hence a marked right-to-left transpulmonary shunt can result when the nondependent lung is not ventilated. However, during one-lung ventilation (OLV), hypoxic pulmonary vasoconstriction (HPV) in the nonventilated lung can reduce the blood flow to that lung by 50% and consequently reduce the shunt to about 20%–24% (1,2).

The present report illustrates that, in two patients with a patent ductus arteriosus (PDA), OLV is associated with Pa_{O_2} above 400 mm Hg at an F_{IO_2} of 1.0, denoting a significantly lower shunt fraction. This response suggests that HPV may be exaggerated in patients with PDA.

Case 1

A 26-yr-old, 54-kg woman with a PDA on echocardiography was scheduled for ligation of the PDA. Chest x-ray and electrocardiogram were normal. Cardiac catheterization confirmed the diagnosis of PDA with a left-to-right shunt and a pulmonary to systemic flow ratio of 2 to 1. Oxygen saturation was 88% in the pulmonary artery and 82% in the right ventricle (RV). Pulmonary artery pressure was 21/4 mm Hg, and RV pressure was 35/0–1 mm Hg (Table 1).

The patient was premedicated with 5 mg morphine, 0.3 mg scopolamine, and 25 mg promethazine intramuscularly 1 h before induction of anesthesia. Before induction, a radial arterial catheter was inserted for arterial blood sampling and continuous blood pressure monitoring. Anesthesia was induced with 5 mg/kg thiopental followed by 1.5 mg/kg succinylcholine. The trachea was intubated with a right-sided, small-sized Robertshaw double-lumen tube. Inflation of the tracheal and bronchial cuffs, as well as checking of the tube for proper replacement, was carried out. Anesthesia was maintained with 1% halothane in 100% oxygen (O_2) supplemented with 2 μg/kg fentanyl and 0.1 mg/kg pancuronium. Two-lung ventilation was continued. The patient was placed in the right lateral-decubitus position. Ten minutes after TLV, blood gas tensions were measured. A left thoracotomy was performed. Before opening the pleura, the tracheal side of the connector was clamped and the tracheal lumen was left open to the atmosphere. When the pleura was opened, the left lung was compressed and completely collapsed, and OLV was started using 1% halothane in 100% O_2. Ten minutes later and before ligation of the PDA,

Table 1. Cardiac Catheterization Data in Case 1 Showing Oxygen Saturation and Pressures

Site	O_2 saturation (%)	Pressure (mm Hg)
RA	85	12/3
RV	82	35/0–1
PA	88	21/4
AO	95	104/61

RA, right atrium; RV, right ventricle; PA, pulmonary artery; AO, aorta.

Received from the Department of Anesthesiology, American University of Beirut, Beirut, Lebanon. Accepted for publication August 14, 1990.

Address correspondence to Dr. Baraka, Department of Anesthesiology, American University of Beirut, 850 Third Avenue, 18th floor, New York, NY 10022.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 2. Arterial Blood Gas Tensions in Case 1 During Two-Lung Ventilation and During and After One-Lung Ventilation

Ventilation	F_{IO_2}	Pa_{O_2} (mm Hg)	P_{CO_2} (mm Hg)	pH	BD (mEq/L)	HCO_3^- (mEq/L)	O_2 saturation (%)
TLV	1.0	608	28	7.47	−2.6	20	99.9
OLV (before ligation)	1.0	594	38	7.37	−2.7	21.8	99.9
OLV (after ligation)	1.0	554	43	7.32	−3.5	22	99.9
TLV	1.0	529	35	7.39	−2.7	21.4	99.9

BD, base deficit; OLV, one-lung ventilation; TLV, two-lung ventilation.

Table 3. Cardiac Catheterization Data in Case 2 Showing Oxygen Saturation and Pressures

Site	O_2 saturation (%)	Pressure (mm Hg)
RA	81	10[a]
RV	80	50/20
PA	86	36/12
AO	96	120/80

Abbreviations as in Table 1.
[a]Mean value.

blood gas tensions were again measured and repeated yet again 10 min after ligation of the PDA. The chest was closed and TLV was resumed. Another arterial blood sample was obtained 10 min after TLV.

Table 2 shows arterial gas tensions during OLV before and after ligation of PDA, as compared with those obtained during TLV. During OLV the Pa_{O_2} was 594 mm Hg before ligation of the PDA and 554 mm Hg after the ligation, levels that correspond respectively to 4% and 6% shunt as predicted from the isoshunt lines (3).

Case 2

This 24-year-old, 58-kg woman was also scheduled for ligation of a PDA. Electrocardiogram and chest x-ray were normal. Oxygen saturation was 86% in the pulmonary artery and 80% in the RV. Pulmonary artery pressure was 36/12 mm Hg and RV pressure was 50/20 (Table 3).

The patient was premedicated with 60 mg meperidine, 0.6 mg atropine, and 25 mg promethazine intramuscularly 1 h before induction of anesthesia. Anesthesia was induced with 5 mg/kg thiopental followed by 1.5 mg/kg succinylcholine and tracheal intubation with a right-sided, small-sized Robertshaw double-lumen tube, which was properly checked. Anesthesia was maintained with nitrous oxide in oxygen (2:1) supplemented with 0.5% halothane and 0.1 mg/kg pancuronium. The patient was placed in the right lateral-decubitus position and TLV was continued. Within 15 min arterial gas tensions were measured at a time when F_{IO_2} was 0.33. As in case 1, a left thoracotomy was performed, OLV was initiated with inspired 1% halothane in 100% O_2 and blood gas tensions were again analyzed. Two-lung ventilation was resumed using F_{IO_2} of 0.33 and another arterial blood sample was obtained. Table 4 shows the blood gas tensions during OLV and during TLV. During OLV the Pa_{O_2} was 428 mm Hg, which corresponds to a shunt of approximately 12% as detected from the isoshunt line (3).

Discussion

One-lung ventilation creates a right-to-left transpulmonary shunt through the nonventilated lung. However, HPV in the hypoxic lung diverts blood toward the ventilated lung (1,2), thereby decreasing the shunt from about 40%–50% to 20%–25%.

The amount of disease in the nonventilated lung is a significant determinant of the magnitude of the shunt. A higher shunt through the nonventilated lung is more likely to occur in patients who require thoracotomy for nonpulmonary disease (4). However, the present report shows that, in two patients

Table 4. Arterial Blood Gas Tensions in Case 2 During Two-Lung Ventilation and During and After One-Lung Ventilation

Ventilation	F_{IO_2}	Pa_{O_2} (mm Hg)	P_{CO_2} (mm Hg)	pH	BD	HCO_3^- (mEq/L)	O_2 saturation (%)
TLV	0.33	188	32	7.44	−2	21.4	99.5
OLV	1.0	428	30	7.48	−0.2	22.6	99.9
TLV	0.33	168	31	7.45	−1	21.9	99.4

Abbreviations as in Table 2.

with no pulmonary disease who required thoracotomy for ligation of a PDA, OLV was associated with Pa_{O_2} levels ranging from 428 to 594 mm Hg, denoting a shunt of only about 4%–12%. The high Pa_{O_2} was present before and after ligation of the PDA, and hence it cannot be attributed to the high oxygen saturation in the shunted blood, but may be secondary to an exaggerated HPV response. Also, HPV is usually blunted rather than potentiated by increasing the mixed venous oxygen tension (5) or the pulmonary vascular pressure (6,7).

Patients with a large PDA or a large unrestricted ventricular septal defect will have developmental anomalies of the pulmonary vasculature that include failure of the normal regression of perinatal musculature and extension of muscle peripherally, as well as medial hypertrophy (8). This may explain why these patients may exhibit an abnormal increase of pulmonary vascular resistance in response to exercise or stress (9,10). Also, it may result in an exaggerated HPV response to alveolar hypoxia.

In conclusion, the present report shows that, in two adult patients with PDAs, OLV with 100% O_2 is associated with Pa_{O_2} levels exceeding 400 mm Hg, denoting a shunt of only about 10%. This may be attributed to an exaggerated HPV response in these patients.

References

1. Benumof JL. Isoflurane anesthesia and arterial oxygenation during one-lung ventilation. Anesthesiology 1986;64:419–22.
2. Benumof JL. One-lung ventilation and hypoxid pulmonary vasoconstriction. Implications for anesthetic management. Anesth Analg 1985;64:821–33.
3. Lawler PGP, Nunn JF. A reassessment of the validity of the isoshunt graph. Br J Anaesth 1984;56:1325–35.
4. Kerr JH, Smith AC, Prys-Roberts C, Meloche R, Föex P. Observations during endobronchial anesthesia. II. Oxygenation. Br J Anaesth 1974;46:84–92.
5. Marshall C, Marshall B. Influence of perfusate P_{O_2} on hypoxic pulmonary vasoconstriction in rats. Circ Res 1983;52:69–96.
6. Benumof JL, Wahrenbrock EA. Blunted hypoxic pulmonary vasoconstriction by increased lung vascular pressures. J Appl Physiol 1975;38:846–50.
7. Malmkvist G, Fletcher R, Nordström, Werner O. Effects of lung surgery and one-lung ventilation on pulmonary artery pressure, venous admixture and immediate postoperative lung function. Br J Anaesth 1989;63:696–701.
8. Burrows FA, Rabinovitch M. The pulmonary circulation in children with congenital heart disease: morphologic and morphometric considerations. Can Anaesth Soc J 1985;32:364–73.
9. Maron BJ, Redwood DR, Hirshefield FW Jr, et al. Postoperative assessment of patients with ventricular septal defect and pulmonary hypertension. Response to intense upright exercise. Circulation 1973;48:864–70.
10. Reid LM, Stevenson JG, Coleman EN, et al. Moderate to severe hypertension accompanying patent ductus arteriosus. Br Heart J 1964;26:60–5.

ANESTH ANALG
1991;72:241–4

A Supraclavicular Lateral Paravascular Approach for Brachial Plexus Regional Anesthesia

S. S. Moorthy, MD, Steven I. Schmidt, MD, Stephen F. Dierdorf, MD,
Stephen H. Rosenfeld, MD, and Jonathan M. Anagnostou, MD

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—brachial plexus (paravascular).

Regional anesthesia for surgery on the upper extremity has distinct advantages over general anesthesia in certain patients. Regional anesthesia produces fewer systemic side effects than does general anesthesia and provides postoperative pain relief. There are several approaches to brachial plexus anesthesia, including interscalene, supraclavicular, subclavian perivascular, infraclavicular, and axillary techniques (1–4). The historical development of brachial plexus anesthesia has been thoroughly reviewed (1).

The traditional supraclavicular approach to the brachial plexus requires needle insertion in a caudad direction perpendicular to the brachial plexus. That approach also directs the needle toward the first rib and close to the pleura thereby running the risk of producing a pneumothorax (5). Proper position of the needle occurs when a paresthesia is elicited or loss of resistance is felt as the needle enters the sheath. Further advancement of the needle can penetrate the pleura or will cease when the first rib is encountered (1,3). The subclavian perivascular technique is done by inserting the needle at the lower end of the interscalene groove, directing the needle caudad, eliciting paresthesia, and injecting local anesthetic solution (2). The incidence of pneumothorax is minimized by this technique.

We propose in this article a modified supraclavicular approach (lateral paravascular approach) that will minimize the risk of pneumothorax and enhance the likelihood of successful anesthesia. The advantages and limitation of a supraclavicular brachial plexus block have been discussed elsewhere (6).

Anatomy

A major portion of the brachial plexus is located parallel and lateral to the third part of the subclavian and first part of the axillary artery, just above and below the clavicle, respectively. Consequently, the third part of the subclavian artery is an important landmark for performing brachial plexus anesthesia using the supraclavicular lateral paravascular approach. The subclavian artery after its origin travels upward and laterally above the clavicle, behind the sternocleidomastoid to the medial border of the anterior scalene muscle (first part), and then deep to the anterior scalene muscle (second part). The third part of the subclavian artery extends from the outer border of the anterior scalene muscle laterally and caudally to the outer border of the first rib, where it becomes the first part of the axillary artery (7). The upper two trunks and their roots of the brachial plexus are superior and posterior to the second part of the subclavian artery. The terminal part of the subclavian artery lies behind the clavicle near its midpoint. At this level the inferior trunk of the brachial plexus is posterior to the third part of the subclavian artery. The upper two trunks are superior and lateral to the subclavian artery. The first rib and pleura are located posterior, medial, and inferior to the subclavian artery. The divisions of the brachial plexus encircle the first part of the axillary artery to form the cords.

The Modified Technique (Lateral Paravascular Approach)

To reduce the risk of pneumothorax, we have modified the supraclavicular approach to the brachial plexus following the anatomic landmarks as diagrammed in Figure 1. The patient is placed in the supine position with the back elevated 5–8 cm in order to accentuate the clavicle and sternocleidomas-

---

Received from the Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana. Accepted for publication September 11, 1990.

Address correspondence to Dr. Moorthy, 1120 South Drive, Fesler Hall 204, Indianapolis, IN 46202-5115.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

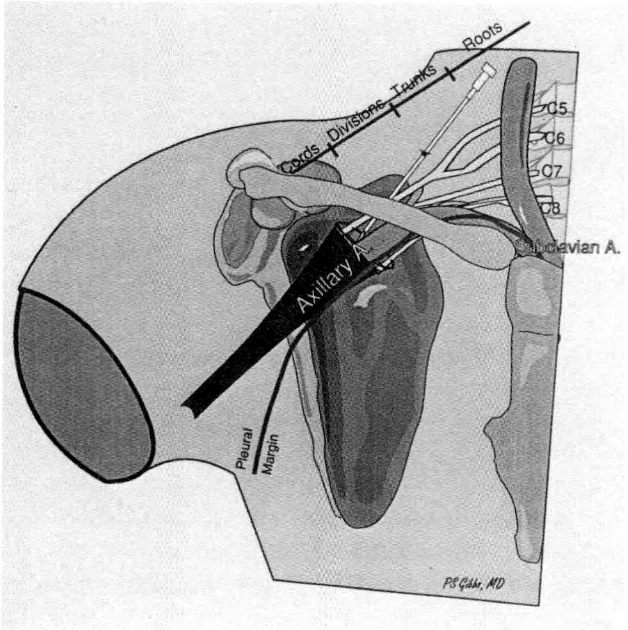


Figure 1. The upper roots of the brachial plexus are superior and posterior to the second part of the subclavian artery. The upper roots and upper two trunks are superior, lateral, and slightly posterior to the third part of the subclavian artery. The divisions of the trunks and the origin of the cords are closely related to the first part of the axillary artery. The stimulating needle for a lateral paravascular injection is placed 2 cm superior and posterior to the clavicle, and 1 cm lateral and parallel to the third part of the subclavian artery and the first part of the axillary artery. The needle is advanced inferiorly and laterally toward the axilla and posteriorly until the upper two trunks or their divisions are encountered, as evidenced by movement of the elbow or forearm. The local anesthetic is injected after a negative aspiration once motor activity is elicited.

toid. The ipsilateral arm is placed at the side and the head is rotated to the contralateral side to an angle of 45° from midline. The subclavian artery (third part) above the clavicle at the lower part of the posterior border of sternocleidomastoid and the first part of the axillary artery below the clavicle are identified with a Doppler flow probe and marked with an indelible marker. The line joining these two points marks the course of the subclavian-axillary artery, the axillary artery coursing to the axilla downward and outward. At this level the upper and middle trunks of the brachial plexus are superior to and lateral to the artery. A skin wheal is raised with a small bore needle and local anesthetic 2 cm superior to and behind the clavicle, and 1 cm lateral to the third part of the subclavian artery marking. At this point a skin puncture is made with an 18-gauge needle to facilitate passage of a stimulating needle. A 5-cm, 24- or 22-gauge Teflon-coated stimulating needle (Stimuplex; B. Braun Melsungen AG, Germany) attached to a nerve stimulator (Stimuplex S; Burron Medical Inc., Bethlehem, Pa.) is passed through the skin wheal. The needle is advanced along and parallel to the surface marking of the subclavian artery, caudally, laterally, and posteriorly, the tip of the needle being directed toward the axilla. The nerve stimulator is set at a current of 0.2–0.5 mA at a frequency of 2 Hz. As the stimulating needle pierces the sheath of the brachial plexus, posterior to the clavicle, motor activity in the upper extremity occurs. When shoulder muscle or pectoral muscle activity is seen, the needle is further advanced to obtain elbow, forearm, wrist, or finger motor activity. The tip of the needle lies behind and just below the clavicle lateral to the first part of the axillary artery. When the motor activity is elicited, the needle is fixed, and, after aspiration, 50 mL of local anesthetic (5 mg/kg mepivacaine or 3 mg/kg bupivacaine) with or without epinephrine (1:200,000) is injected. The earliest evidence of successful brachial plexus blockade (onset time, 3–5 min) is that the patient's arm "falls off" laterally.

Materials and Methods

We analyzed a total of 132 brachial plexus blocks during a period of 12 mo (July 1989–June 1990) done in 126 adult patients. Their ages ranged from 22 to 77 yr (mean, 44 yr). There were 124 men and two women. Forty-one patients had end-stage renal disease requiring arteriovenous access surgery, and some received multiple blocks. Fourteen patients had excision of Dupuytren's contracture, six had excision of ganglion cysts at the wrist, and six had release of carpal tunnel syndrome. The remainder of the patients had various orthopedic procedures on the upper extremity. Of the 132 cases of brachial plexus block, 50 were axillary blocks by the transarterial approach and 82 were supraclavicular paravascular brachial plexus blocks as described above. All patients had intercostobrachial nerve block by a subcutaneous wheal in the axilla.

Results

Sixty-one of the 82 cases (72%) of supraclavicular lateral paravascular block produced a good surgical anesthetic. Twelve produced partial brachial plexus block and supplemental local anesthetic was required during surgery. There were nine failures; in these cases general anesthetic was required for the surgery. Forty-three of the 50 cases (80%) of axillary block produced a good surgical anesthetic, and general anesthesia was required in six cases (12%) because of

Table 1. Analysis of 132 Brachial Plexus Blocks Done During 12 Months (1989–1990)

	Lateral paravascular block	Axillary block
Number of cases	82	50
Cases with good anesthesia	61 (72)[a]	43 (86)
Cases requiring supplemental local anesthetic	12 (14.6)	2 (4)
Cases requiring general anesthesia	9 (11)	6 (12)
Complications[b]	0	1

[a] Numbers in parentheses are percentages.

[b] The one complication consisted of convulsions in one case, in the axillary block group; this was successfully treated.

failure of the block (Table 1). The onset time was similar in both groups, between 3 and 5 min, with complete analgesia occurring in 15 min. There was no statistical difference in the failure rate between the paravascular and axillary groups as tested by Wilcoxin's signed rank test ($P = 0.16$).

Discussion

We present a modified successful brachial plexus anesthesia technique in 61 cases via a supraclavicular, lateral paravascular approach not previously described. The subclavian artery could easily be located above the clavicle, lateral to the lower end of the posterior border of the sternocleidomastoid, and the first part of the axillary artery was identified below the clavicle. The line joining these two arterial points runs caudally and laterally toward axilla. The stimulating needle is inserted 2 cm above and behind the clavicle and 1 cm lateral to the subclavian artery and is directed caudally, posteriorly, and laterally toward the axilla, in a direction parallel to the artery. As the needle is advanced posterior to the clavicle, muscular movements in the upper extremity can be observed. If movements of only deltoid or pectoralis major are observed, the needle is further advanced to below the clavicle level or redirected more posteriorly until movements at elbow, forearm, or hand are observed. The tip of the needle is then behind and below the clavicle. The needle is directed away from the thorax, and there is no need to encounter the first rib, minimizing the risk of pneumothorax. The dome of the pleura is medial and inferior to the subclavian artery. The upper brachial plexus is superolateral to the subclavian artery. Consequently, the needle is lateral to and directed away from the pleura, thereby markedly reducing the likelihood of pleural puncture. Motor activity is generally achieved at 0.2–0.5 mA at a frequency of 2 Hz.

Our retrospective analysis of the patients showed that more patients received axillary blocks in 1989, whereas more received lateral paravascular block in 1990. The failure rate associated with the latter decreased as we gained experience with the technique. Failure was more frequent in obese patients and in patients with short necks.

Our technique differs from the subclavian perivascular technique previously described (2). The needle enters the lower part of the interscalene groove above the subclavian artery in the perivascular technique. The needle is then advanced directly caudad until paresthesias are elicited or a palpable "click" with penetration of brachial plexus sheath is felt (2). The needle still can contact the first rib if the needle is advanced caudally, hence potentially approaching the pleura. The lateral paravascular technique is lateral to the artery and does not come into contact with the first rib, and we elicit motor response with the nerve stimulator.

Further, our method differs from the other techniques in that the last part of the subclavian artery and the first part of the axillary artery below the clavicle are identified with a Doppler flow probe, and its course is marked on the skin surface. The Teflon-coated stimulating needle contacts the superior parts of the brachial plexus, contact with the first rib and the upper thorax thereby being avoided. We have found this technique to be highly successful. It requires minimum patient cooperation, and there have been no complications. Failure to achieve motor nerve stimulation is generally due to anterior placement of the needle, and so the needle should be withdrawn and redirected more posteriorly. The intercostobrachial nerve may have to be blocked in the traditional subcutaneous manner.

In conclusion, we describe a successful technique for producing brachial plexus anesthesia using a modified supraclavicular, lateral paravascular approach. We are using this method of brachial plexus block with increasing frequency and success. We use a Doppler flow probe for localizing the subclavian axillary artery and a nerve-stimulating needle for localization of the brachial plexus. We enter the skin 2 cm above and behind the midpoint of the clavicle and 1 cm lateral to the subclavian artery, and direct the needle downward, outward toward the axilla, and behind the clavicle until movements at the elbow, forearm, or fingers are obtained when the local anesthetic is injected. We believe that this approach is safer than the previously described supraclavicular approaches to the brachial plexus block (1,2).

References

1. Winnie AP. Plexus anesthesia. In: Hakansson L, ed. Perivascular techniques of brachial plexus block. Volume 1. Philadelphia: WB Saunders, 1983.
2. Winnie AP, Collins VJ. The subclavian perivascular technique of brachial plexus anesthesia. Anesthesiology 1964;25:353–63.
3. Brand L, Papper EM. A comparison of supraclavicular and axillary techniques for brachial plexus blocks. Anesthesiology 1961;22:226–9.
4. Yasuda G, Hiranto T, Ojima T. Supraclavicular brachial plexus block using a nerve stimulator and an insulated needle. Br J Anaesth 1980;52:409–11.
5. Bridenbaugh PO. Complications of local anesthetic neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. Philadelphia: JB Lippincott, 1988:695–77.
6. Bridenbaugh D. The upper extremity: somatic blockade. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. Philadelphia: JB Lippincott, 1988:387–416.
7. Gray H. Anatomy of the human body. In: Clemente CD, ed. Philadelphia: Lea & Febiger, 1985;694–6.

Nearly Fatal Cardiovascular Collapse During Total Hip Replacement: Probable Coronary Arterial Embolism

William R. Camann, MD, Gerald M. Sacks, MD, Ann G. Schools, MD,
Steven T. Heggeness, MD, Donald T. Reilly, MD, and Mercedes Concepcion, MD

Key Words: EMBOLISM, CORONARY ARTERY. SURGICAL, ORTHOPEDIC—total hip replacement.

Embolic phenomena are a recognized complication of various surgical procedures. Neurosurgical, orthopedic, and obstetric patients may be especially at risk for intraoperative emboli owing to positioning (surgical field above heart), anatomic (open venous sinuses), and surgical (bone manipulation) features unique to such operations. Emboli may consist of air, bone, bone marrow, fat, or thrombus. Venous air emboli (VAE) are particularly common during total hip replacement (THR). Passage of emboli into the pulmonary circulation is associated with recognized sequelae, and entrainment into the arterial system via a right-to-left cardiac communication may result in devastating cerebral, systemic, and/or coronary paradoxical embolism. We report herein an instance of cardiovascular collapse during orthopedic surgery, presumably resulting from paradoxical coronary arterial embolism.

Case Report

A 42-yr-old, 50-kg woman was scheduled for revision of a right THR. She had suffered from juvenile rheumatoid arthritis since age 18 yr and had previously undergone bilateral THR, four subsequent revisions of the left THR, bilateral total knee replacements, and left total elbow replacement. Multiple prior general and regional anesthetics had been uncomplicated, except for difficulty with tracheal intubation. She reported no history of cardiac or pulmonary disorders. Physical examination revealed typical sequelae of severe juvenile rheumatoid arthritis, particularly limited neck mobility and poor mouth opening. No murmur was heard during cardiac auscultation. Pertinent laboratory data were within normal limits.

The patient was brought to the operating room after premedication with 5 mg oral diazepam. After insertion of a peripheral intravenous catheter and application of routine monitors (blood pressure cuff, electrocardiogram, pulse oximeter), an epidural catheter was easily placed at the L3-4 interspace and a sensory level to T-8 obtained with 15 mL of 1.5% etidocaine (Duranest) with 1:200,000 epinephrine. Topical anesthesia of the upper airway preceded relatively easy fiberoptic placement of a 6.5-mm tracheal tube via the right naris. General anesthesia was then induced with thiopental and fentanyl intravenously, and nitrous oxide and isoflurane by inhalation with mechanical ventilation. After the patient was placed in the left decubitus position, the operation proceeded uneventfully for approximately 3.5 h. After an acetabular component was placed, reaming of the femoral shaft was begun. Over a period of a minute, heart rate increased from 80 to 130 beats/min and a 6-mm ST-segment elevation suddenly appeared on electrocardiogram leads II and V_5. Blood pressure was 120/70 mm Hg, oxygen (O_2) saturation (100%), and end-tidal carbon dioxide (CO_2) was 32 mm Hg. No intravenous or epidural drugs had been given for at least 20 min. Nitrous oxide and isoflurane were discontinued, and manual ventilation of the lungs was easily performed. Approximately 2 min later, heart rate abruptly declined to 40 beats/min and blood pressure could not be obtained. Atropine, 0.4 mg, and 10 mg ephedrine were given intravenously. Bradycardia (now 27 beats/min) persisted, and blood pressure remained unobtainable. The surgeons were urged to close the operative site as rapidly as possible, and cardiopulmonary resuscita-

---

Received from the Departments of Anesthesia and Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication September 6, 1990.

Address correspondence to Dr. Camann, Department of Anesthesia, Brigham and Women's Hospital, 75 Frances Street, Boston, MA 02115.

©1991 by the International Anesthesia Research Society

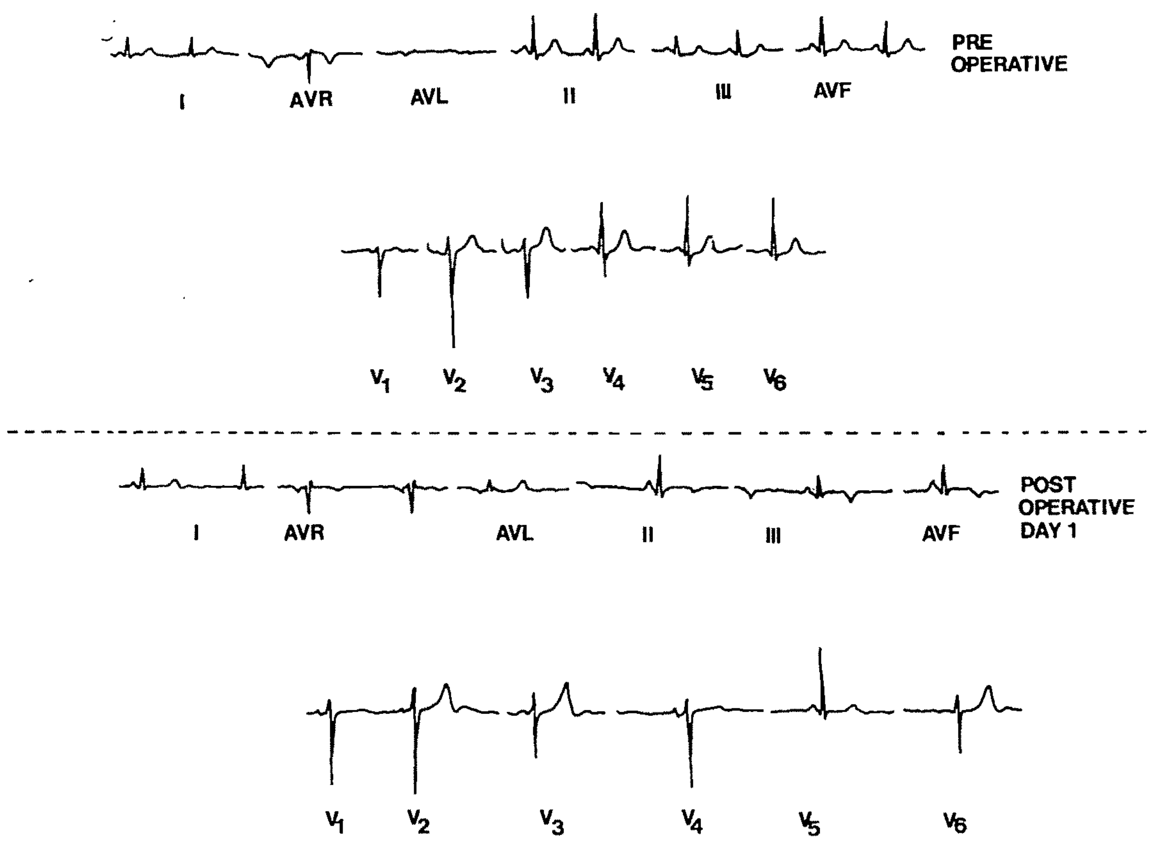


Figure 1. Twelve-lead electrocardiogram preoperatively and on postoperative day 1.

tion was begun with the patient still in the lateral position. Arterial O_2 saturation decreased to 92% and end-tidal CO_2 to 23 mm Hg. Epinephrine, 1 mg IV, was given, and the patient was returned to the supine position. Electrocardiogram revealed ventricular fibrillation, which responded to cardioversion with 300 J, resulting in a supraventricular tachycardia at a rate of 180 beats/min. Blood pressure was now 180/100 mm Hg and O_2 saturation 100%. An arterial catheter was inserted into the right radial artery, and blood gas analysis revealed Pa_{O_2} 446 mm Hg, Pa_{CO_2} 27 mm Hg, pH 7.21, serum potassium 5.3 mEq/L, and hematocrit 26%. Verapamil, 5 mg, was administered intravenously, and heart rate soon decreased to 100 beats/min. Normal breath sounds were heard bilaterally throughout the above episode.

The patient was taken to the recovery room with her trachea still intubated. A 12-lead electrocardiogram showed 3-mm ST-segment elevation in leads II, III, aVF, and V_2-V_6. Chest x-ray showed no acute pathology. Serum electrolyte levels, blood urea nitrogen, and blood glucose were all within normal limits. The trachea was extubated the following morning, and the patient had no recall of events of the previous day. Serum creatinine phosphokinase-MB analysis and serial electrocardiogram readings confirmed the presence of acute inferior myocardial infarction (Figure 1). Cardiac catheterization, performed the following day, revealed normal coronary vascular anatomy, with inferior and septal wall motion abnormalities. Contrast echocardiography, performed on the third postoperative day, demonstrated spontaneous passage of contrast from right to left atria, which was accentuated by Valsalva maneuver. These findings are consistent with either a patent foramen ovale or a small, but hemodynamically insignificant, atrial-septal defect.

Recovery proceeded uneventfully, although a second operation was necessary as the operative site had been rapidly closed and a permanent femoral component had not been placed. Consequently, 2 wk later, the patient returned to the operating room for definitive placement of the permanent hip prosthesis. Monitoring included arterial and central venous catheters and a precordial Doppler stethoscope, as well as other routine monitors. General anesthesia was induced as before with fiberoptic-aided oral intubation. Operation was performed uneventfully with the patient in approximately 30° head-up tilt. The patient was discharged from the hospital in good condition 12 days later.

Discussion

The events that occurred in this case were probably a result of paradoxical embolism into a coronary artery. The hemodynamic deterioration and subsequent cardiac arrest occurred suddenly after several hours of operation and anesthesia in a patient with no prior history of cardiac disease. Electrocardiographic changes immediately before the arrest were suggestive of myocardial ischemia due to acute coronary artery occlusion. The operation (THR) is one known to be associated with emboli consisting of air (1–4), fat (5,6), bone (7), and/or bone marrow and cement (8). Moreover, the occurrence of such emboli is most likely during preparation of the femoral canal for prosthesis insertion (1–4,8), precisely the time at which our patient demonstrated difficulties. Postoperatively, documentation of normal coronary arteries ruled out the possibility of previously undiagnosed atherosclerotic coronary artery disease. Enzymatic and echocardiographic studies were all consistent with acute myocardial infarction, and the presence of an atrial-septal communication was documented. Although hemodynamic collapse can occur due to embolic obstruction of the right ventricular outflow tract and pulmonary ventilation-perfusion mismatch, the first presenting sign in our patient was sudden, profound ST-segment elevation; arterial O_2 desaturation and bradycardia followed thereafter. Thus, coronary arterial embolism seems the most logical explanation for the cardiac arrest.

The etiology of the presumed emboli in our case is unknown. Air may seem a likely source, given the lack of a discrete filling defect on postoperative coronary angiography. However, in the left decubitus position, heavier particulate matter may be more likely to encounter and cross an atrial septal defect, whereas air might tend to remain along the nondependent aspect of the right atrial chamber. It has been suggested (but not proven) that VAE may be more likely to progress to paradoxical emboli during left, rather than right, THR (9). On the other hand, simple reliance on pressure-flow phenomena may be misleading, as transient reversals of atrial pressure gradients during the cardiac cycle may allow paradoxical air emboli to occur even when mean right atrial pressure is lower than mean left atrial pressure (10). Furthermore, the forces of buoyancy associated with position are likely to be overcome by the stronger forces of blood flow within the cardiac chambers (11).

Venous air embolism is known to occur frequently during THR; the reported incidence varies with the particular method of detection utilized. Open venous sinuses in the femoral canal and the decubitus position (with hip above heart) favor air entrainment during this operation. Harvey and Smith reported 16% (4/25) incidence using esophageal stethoscope monitoring (3). Evans et al. found a 67% (4/21) incidence (during reaming of the femoral shaft) using precordial Doppler monitoring, which increased to 100% during insertion of the femoral prosthesis (2). Andersen was also able to detect Doppler changes consistent with VAE in five of six patients, even as air was aspirated from a central venous catheter in four (1). Heinrich et al., using two-dimensional transesophageal echocardiography, were able to detect VAE in 12 of 13 patients during implantation of femoral prostheses (4).

Various methods have been utilized to reduce the likelihood of VAE during THR. Harvey and Smith reported a decrease from 16% to 0% when the femoral shaft was insufflated with CO_2 (3). Evans et al. reduced the incidence from 100% (9/9) to 33% (4/12) when the femoral cement was inserted with an automatic cement gun, rather than with manual instillation (2). Heinrich et al. reduced the incidence from 92% (12/13) to 30% (4/13) with the placement of a venting hole in the femoral shaft (4). The utilization of these modalities varies, and none was used during our case.

A 10%–25% incidence of probe-patent foramen ovale in the general population (12) implies that many patients undergoing THR are at risk for paradoxical emboli. The relative low morbidity in THR, however, suggests that not all patients at risk actually have clinically significant episodes of this phenomenon. Our case demonstrates the profound hemodynamic sequelae that may ensue when paradoxical emboli develop. Whether routine use of preoperative contrast echocardiography, central venous catheterization, and/or more sensitive means of embolic detection (i.e., precordial Doppler or transesophageal echocardiography) should be employed in all cases of THR remains at the discretion of the individual practitioner.

The authors thank Leroy D. Vandam, MD, for his kind review of the manuscript.

References

1. Andersen KH. Air aspirated from the venous system during total hip replacement. Anaesthesia 1983;38:1175–8.

2. Evans RD, Palazzo MGA, Ackers JWL. Air embolism during total hip replacement: comparison of two surgical techniques. Br J Anaesth 1989;62:243–7.
3. Harvey PB, Smith AJA. Prevention of air emboli in hip surgery: femoral shaft insufflation with carbon dioxide. Anaesthesia 1982;37:714–7.
4. Heinrich H, Kremer P, Winter H, Worsdorfer O, Anhfeld FW. Transesophageal two-dimensional echocardiography during total hip replacement. Anaesthesist 1985;34:118–23.
5. Watson JT, Stulberg BN. Fat embolism associated with cementing of femoral stems designed for press-fit application. J Arthroplasty 1989;4:133–7.
6. Hagley SR, Lee FC, Blunbergs PC. Fat embolism syndrome with total hip replacement. Med J Aust 1986;145:541–3.
7. Bras JM, Veraart BE. Pulmonary bone embolism after total hip replacement. J Bone Joint Surg (Br) 1980;62:22–4.
8. Svartling N. Detection of embolized material in the right atrium during cementation in hip arthroplasty. Acta Anaesthesiol Scand 1988;32:203–8.
9. Young C, Wright DJ. Paradoxical air embolism during hip surgery (letter). Anaesthesia 1986;41:1162.
10. Black S, Cuchiara RF, Nishimura RA, Michenfelder JD. Parameters affecting occurrence of paradoxical air embolism. Anesthesiology 1989;71:235–41.
11. Butler BD, Laine GA, Leiman BC, et al. Effect of Trendelenburg position on the distribution of arterial air emboli in dogs. Ann Thorac Surg 1988;45:198–202.
12. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17–20.

Brainstem Toxicity With Reversible Locked-In Syndrome After Intrascalene Brachial Plexus Block

Zia Durrani, MD, and Alon P. Winnie, MD

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—brachial plexus, interscalene. COMPLICATIONS, TOXICITY—arterial injections. ANESTHETICS, LOCAL—toxicity.

The interscalene technique for blocking the brachial plexus introduced by Winnie in 1970 (1) is widely used for a variety of procedures on the upper extremities. Various complications following interscalene block, such as systemic toxicity, epidural (2) and total spinal block (3), Horner's syndrome (4), and recurrent laryngeal nerve block (5) have been previously reported. We report a reversible locked-in syndrome secondary to brainstem depression due to inadvertent injection of local anesthetics into the vertebral artery during interscalene block. "Locked-in syndrome describes a state in which selective supranuclear motor deefferentiation in the brainstem produces paralysis of all four extremities and lower cranial nerves without interfering with consciousness. The voluntary motor paralysis prevents the subjects from communicating by words or by body movement" (6). Vertical eye movements and blinking are the only voluntary movements that can be performed. Because of a combination of tetraplegia and aphonia, these patients are considered to be unconscious or comatose even though they are otherwise fully conscious and aware of internal and external stimuli (6).

Case Report

A 29-yr-old, 75-kg black woman with end-stage renal disease was scheduled for an arteriovenous Gortex graft placement in the right forearm. Past medical history included hypertension and pneumonia. Previous surgical procedures included tubal ligation, appendectomy, multiple arteriovenous graft placements, and mediastinal hematoma drainage secondary to a Quentin catheter placement. She had received both general and brachial plexus anesthesias without any anesthetic sequelae. Physical examination was unremarkable except for grade III/IV systolic murmur and blood pressure of 170/95 mm Hg. Preoperative laboratory values were normal (electrocardiogram, chest x-ray) except for a blood urea nitrogen level of 45 mg/dL, a creatinine level of 12.5 mg/dL, and an hematocrit of 25%.

Because the patient had previously received brachial plexus block for arteriovenous graft and had requested the same for the current procedure, an interscalene brachial plexus block was planned. She was premedicated with 10 mg of intramuscular morphine sulfate and was given 100 mg of intravenous hydrocortisone. The usual monitoring devices were applied, including blood pressure cuff and electrocardiogram. Blood pressure was 150/100 mm Hg, heart rate 75 beats/min, and respiratory rate 16 breaths/min. With the patient in the supine position, after sterile preparation, a 22-gauge, 4-cm, blunt-bevelled needle was inserted into the interscalene groove using Winnie's interscalene technique (1). The needle was advanced until the patient experienced a paresthesia in the right elbow area. Location of the needle was reconfirmed using a nerve stimulator. After negative aspiration, it was noted that the direction of the needle, instead of "mesiad, dorsad, and slightly caudad," was directly medial. However, because of appropriate paresthesia, it was considered that the position of the needle was acceptable. After negative aspiration for blood, air, or fluid, an anesthetic mixture containing 1% mepivacaine, 0.2% tetracaine with 1:200,000 epinephrine, and 1 mEq/10 mL bicarbonate was slowly injected. During the injection, frequent aspirations were performed without any return of blood. The patient received a total of 40 mL of this

---

Received from the Departments of Anesthesiology, the Rush-Presbyterian-St. Luke's Medical Center, and the University of Illinois Medical Center, Chicago, Illinois. Accepted for publication September 7, 1990.

Address correspondence to Dr. Durrani, Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, 739 Jelke, 1750 West Harrison, Chicago, IL 60612.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

mixture, and the needle was withdrawn. Within 30 s after the completion of the injection, the patient became apneic and was unable to follow verbal commands to breathe, move her limbs, or vocalize. However, she was able to open and close her eyes and also to move her eyes in a vertical direction. Within another 30 s, her blood pressure and pulse decreased to 80/50 mm Hg and 40 beats/min, respectively. Two minutes after that, twitching started around her mouth, followed by a generalized seizure. During the seizure, the patient's right arm remained motionless. Immediately after the apnea, she was given 100% oxygen via a mask, and, after the onset of the seizure, she was given 250 mg of thiopental and 140 mg of succinylcholine (both intravenously), followed by tracheal intubation and mechanical ventilation. Her blood pressure and pulse were 80/50 mm Hg and 40 beats/min, respectively. These returned to near the original values after three intravenous doses of 5 mg ephedrine and one dose of 0.4 mg atropine. Arterial blood gas tensions immediately after intubation included a Pco_2 of 62 mm Hg, Po_2 of 362 mm Hg, and pH of 7.04. About 20 min after intubation, the patient started to breathe spontaneously, and, in 10 more minutes, she woke up and was extubated. Her hemodynamic status remained stable. Upon examination, she had dense sensory and motor block of the right brachial plexus from C-5 to T-1. Upon interview, she claimed that throughout the preceding events she was able to understand the "commotion" and understood the verbal commands, but was unable to move her extremities or talk. Repeated measurement of arterial blood gas tensions gave normal values. The operation was canceled at the request of the surgeon. The brachial plexus block lasted for over 4.5 h. The surgery was performed the next day with local infiltration and intravenous sedation.

Discussion

"Locked-in syndrome" is an akinetic state that is the result of lesions in the central and/or ventral pons, but the tegmentum and, therefore, the reticular-activating system and supranuclear ocular motor nuclei are spared. Blinking and vertical eye movements are the only means of communication (6). Usually, locked-in syndrome is caused by a cerebrovascular accident of the brainstem and carries a high mortality; the majority of those who survive remain in a permanent akinetic state. Reversible locked-in syndrome with some residual sequelae after the basilar artery spasm has also been previously reported (7). In our case, the locked-in syndrome was transient and totally reversible. The patient appeared to have lost consciousness; however, on closer examination, she was attempting to communicate by blinking and vertical eye movements. After recovering from the episode, she said she remained totally aware during the initial period although, in spite of her efforts, she could not move or talk.

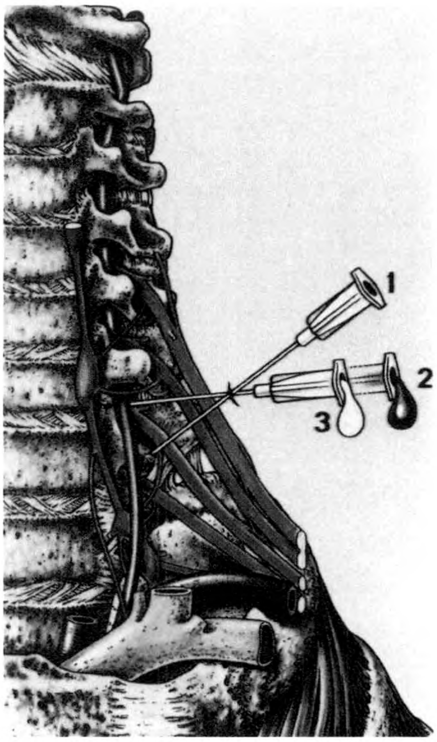


Figure 1. *1*, Correction direction; *2*, vertebral arterial injection; and *3*, epidural subarachnoid space injection. Reprinted with permission from Winnie AP (Plexus anesthesia. Volume I. Philadelphia: W.B. Saunders, 1983).

Although the vertebral artery is outside the brachial plexus sheath, it is in close vicinity, and if the needle is improperly directed in the medial direction during an interscalene block instead of "mesiad, dorsad, and slightly caudad" (4), it can enter the epidural space, subarachnoid space, or the vertebral artery (see Figure 1). Negative aspiration before injection is not a reliable indicator of the needle's position (8). Because blood flow to the brainstem is almost entirely supplied by the vertebral basilar system, even a minute quantity of a local anesthetic injected into the vertebral artery could result in brainstem toxicity. Korevaar reported that a dose as small as 18 mg (240 μg/kg) of lidocaine, when injected directly into the vertebral artery of a 75-kg subject, can cause convulsions (8). However, even this dose is an overestimate because the calculation was based on the assumption that perhaps 25% of the total cerebral blood flow passes through each vertebral artery,

Table 1. Toxic Dose of Local Anesthetics: Systemic Circulation Versus Cerebral Circulation

Local anesthetic	Min IV toxic dose in humans (mg/kg)	Estimated intravertebral artery toxic dose (μg/kg)[a]	Estimated intracarotid artery toxic dose (mg/kg)[a]
Procaine	19.2	288	2.592
Chloroprocaine	22.8	342	3.078
Tetracaine	2.5	37.5	0.337
Lidocaine	6.4	96	0.864
Mepivacaine	9.8	147	1.323
Bupivacaine	1.6	24	0.216
Etidocaine	3.4	51	0.459

Min IV, minimum intravenous (Reference 11).

[a] Based on the cerebral circulation being 15% of the total cardiac output and vertebral basilar circulation being 10% of the total cerebral circulation.

whereas only 10% of the total cerebral blood flow passes through the entire vertebral basilar system (9). Also, because of the confluence of the two vertebral arteries into a single basilar artery, the vertebral basilar system is considered a single entity and, in fact, in 10% of the cases, the vertebral artery is so small that the other vertebral artery is essentially the only vessel supplying the brainstem (10). Based on the above physiologic facts, even a smaller dose such as 7.2 mg (96 μg/kg) of lidocaine in a 75-kg patient, when injected directly into the vertebral artery, could produce toxic effects. In our patient, an inadvertent intravertebral artery injection of only 2.5 mg of tetracaine or 11.02 mg of mepivacaine (less than 1 mL of the local anesthetic mixture) could have caused the brainstem depression (see Table 1). Because of the close vicinity of the stellate ganglion and Chassaignac tubercle to the vertebral artery, as well as the dorsal direction of the needle, stellate ganglion block can represent a greater risk of inadvertent intravertebral arterial injection than interscalene block, and, in the literature, there are multiple reports of "brainstem toxicity" after a stellate ganglion block (8,12–15). Closer scrutiny of these case reports reveals that although not labeled as "locked-in syndrome," many fit that description.

Alternate explanations of the locked-in syndrome in this patient could be spasm or external compression of the vertebral artery. External bathing of the vertebral artery with epinephrine-containing solution can cause spasm of this vessel (16). Carotid bruit after interscalene block has been reported due to extrinsic compression by the large volume of the local anesthetic (17). It is possible that similar mechanisms can cause vertebral artery compression. However, occlusion of the vertebral artery low in the neck is usually compensated for by anastomotic flow to the upper part of the artery via the thyrocervical, deep cervical, and occipital arteries.

Direct application of a local anesthetic to the brainstem causes profound hypotension, bradycardia, and arrhythmia (18). A combination of sudden and profound cardiovascular collapse, direct toxic effect of mepivacaine or tetracaine on the brainstem, and apnea with ensuing respiratory acidosis could have precipitated the seizure seen in our patient.

Because of the presence of a seizure followed by rapid and total recovery in this patient, an inadvertent spinal block is highly unlikely. Inadvertent epidural block is also unlikely because such a block has gradual onset and has been reported to be bilateral, and because the mixture of mepivacaine and tetracaine should give a long-lasting block.

Systemic toxicity, even though a remote possibility in this patient, is worth considering. To obtain systemic toxic effects, a major portion of the mixture in this patient would have had to have been injected intravascularly; however, the patient had a profound brachial plexus block that lasted over 4 h, indicating that most of the local anesthetic remained extravascular. Moreover, the prodromal symptoms and subsequent signs of systemic toxicity are quite different from what was observed in this patient.

In conclusion, we describe a vertebral artery injection during an interscalene brachial plexus block. We emphasize that if the appropriate technique is not used, serious complications, including total spinal or epidural block, and locked-in syndrome can occur as a result of a medially misdirected needle. Successful treatment of these complications depends upon appropriate and early diagnosis followed by aggressive management including oxygenation, ventilation, and vasopressors.

References

1. Winnie AP. Interscalene brachial plexus block. Anesth Analg 1970;49:455–66.
2. Kumar A, Battit GE, Froese AB, Long MC. Bilateral cervical and thoracic epidural blockade complicating interscalene brachial block: a report of two cases. Anesthesiology 1971;35:650–2.
3. Ross S, Scarborough CD. Total spinal anesthesia following brachial plexus block. Anesthesiology 1973;39:958.
4. Winnie AP. Plexus anesthesia. Volume 1. Philadelphia: WB Saunders, 1983:242.
5. Seltzer JL. Hoarseness and Horner's syndrome after interscalene brachial plexus block. Anesth Analg 1977;56:585–6.
6. Plum F, Posner JB. The diagnosis of stupor and coma. 3rd ed. Philadelphia: FA Davis, 1980:9.
7. Ebinger G, Huyghes L, Corne L, Aelbrecht W. Reversible "locked-in syndrome." Intens Care Med 1985;11:218–9.

8. Korevaar WC, Burney RG, Moore PA. Convulsion during stellate ganglion block: a case report. Anesth Analg 1979;58: 329–30.
9. Youman JR. Neurological surgery. 2nd ed. Philadelphia: WB Saunders, 1982:795.
10. Adam RD, Victor M. Principles of neurology. 3rd ed. New York: McGraw Hill Book Company, 1985:586–8.
11. Savarese JJ, Covino BG. Basic and clinical pharmacology of local anesthetic drugs. In: Miller RD, eds. Anesthesia. 2nd ed. New York: Churchill Livingstone, 1986:1003.
12. Whitehurst L, Harrelson JM. Brain-stem anesthesia: an unusual complication of stellate ganglion block. J Bone Joint Surg 1977;59A:541–2.
13. Szeinfeld M, Laurencio M, Pallares VS. Total reversible blindness following attempted stellate ganglion block. Anesth Analg 1981;60:689–90.
14. Kozody R, Ready LB, Barsa JE, Murphy TM. Dose requirement of local anaesthetic to produce grand mal seizure during stellate ganglion block. Can Anaesth Soc J 1982;29:489–91.
15. Scott DL, Ghia JN, Teeple E. Aphasia and hemiparesis following stellate ganglion block. Anesth Analg 1983;62:1038–40.
16. Handa J, Meyer JS, Yoshida K. Regional pharmacologic responses of the vertebral and internal carotid arteries. J Pharmacol Exp Ther 1966;152:251–64.
17. Siller JN, Lierf PL, Davis JF. A new complication of interscalene brachial plexus block. Anesthesiology 1973;38:590–1.
18. Thomas RD, Behbehani MM, Coyle DE, Denson DD. Cardiovascular toxicity of local anesthetics: an alternative hypothesis. Anesth Analg 1986;65:444–50.

ANESTH ANALG 253
1991;72:253-6

Back Pain in Volunteers After Epidural Anesthesia With Chloroprocaine

James M. Hynson, MD, Daniel I. Sessler, MD, and Beth Glosten, MD

Key Words: ANESTHETICS, LOCAL—chloroprocaine, lidocaine. ANESTHESIA, EPIDURAL—complications: back pain.

We recently noted a high incidence of severe back pain in volunteers participating in a study of thermoregulation during epidural anesthesia. Each of these individuals received a volume of 3% chloroprocaine sufficient to achieve a midthoracic blockade level. On recovery from anesthesia, and for several hours thereafter, four of five volunteers experienced unrelenting, severe, spasmodic lumbar pain. We had not observed any similar pain in our previous epidural studies and therefore present our experience with back pain after epidural injections in volunteers not undergoing surgery.

Methods

Nineteen young, healthy, nonpregnant volunteers participated in one of three similar sequential studies of shivering and hypothermia during lumbar epidural anesthesia. All three studies were completed within a 1-yr period and were performed with the approval of the University of California, San Francisco Committee on Human Research and with written informed consent.

In each subject, an epidural catheter was passed through a Tuohy needle after identification of the epidural space at L3–4 using loss of resistance to air. Subjects reported no significant discomfort during placement of the needle or catheter, and no cerebrospinal fluid was aspirated. Subjects were then asked to position themselves comfortably on a well-padded operating room table that was adjusted to provide slight flexion at the hips and knees (chaise-lounge position). Lumbar support was provided by a folded blanket if requested. Throughout each study, we ascertained positional comfort and adjusted the operating room table if necessary. Back pain during the study was assessed as mild, moderate, or severe.

All volunteers were minimally clothed and studied in a cool room (~20°C). Tympanic membrane temperatures were measured using Mon-a-Therm thermocouples. Shivering was ranked by observers as absent, mild, or vigorous.

Our first two studies tested the effects of epidural injectate temperatures on shivering. In each volunteer, 4 mL of 0.75% bupivacaine was infiltrated into the skin and paraspinous muscle before introducing the 16-gauge Tuohy needle and epidural catheter. One group of four volunteers (two men) received a series of three 80-mL injections of saline, one warm (54°C) and two cold (0°C) at 5 mL/min (1). Injections were given at 2-h intervals. Shivering was induced by application of a cold circulating water blanket (5°C) during one phase of this study. The second group of 10 volunteers (six men) received two 30-mL injections of 1% lidocaine, one warm (50°C) and one cold (0°C) at 15 mL/min (2). A recovery period of 3 h transpired between injections at different temperatures. In four of these 10 subjects, the lower extremities were warmed using a forced-air warmer (Bair Hugger, Augustine Medical Inc.). The protocol in both these studies required approximately 7 h of study for each subject.

Our third study investigated mechanisms causing central hypothermia during epidural anesthesia. The skin was infiltrated with 2 mL of 1% lidocaine before introducing the 18-gauge Tuohy needle and epidural catheter in five volunteers (one woman). Each was given a 3-mL test dose of 3% chloroprocaine (Nesacaine-MPF), followed by an initial bolus of

---

Supported by National Institutes of Health grant R29 GM39723 and Augustine Medical, Inc.

Presented at the Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 1990.

Received from the Department of Anesthesia, University of California, San Francisco, California, and the Department of Anesthesiology and Critical Care, University of Chicago, Chicago, Illinois. Accepted for publication September 25, 1990.

Address correspondence to Dr. Sessler, Department of Anesthesia, Room C-450, University of California, San Francisco, CA 94143-0648.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Epidural Injectate, Back Pain, and Morphometric Data

Group	Pain (yes/no)	Gender (M/F)	Age (yr)	Weight (kg)	Height (cm)	Volume injected Initial (mL)	Volume injected Total (mL)	Segmental level of anesthesia
Saline	0/4	2/2	31 ± 4	58 ± 4	164 ± 5	80 ± 0	240 ± 0	—
Lidocaine	1/9	6/4	29 ± 4	64 ± 10	164 ± 8	30 ± 0	60 ± 0	T8 ± 2
Chloroprocaine	4/1	4/1	23 ± 2	75 ± 11	177 ± 9	38 ± 8	56 ± 8	T3 ± 1

Data are presented as mean ± SD. Groups were statistically different in terms of age (chloroprocaine vs lidocaine, chloroprocaine vs saline), weight (all groups), height (chloroprocaine vs lidocaine, chloroprocaine vs saline), initial volume (all groups), total volume (chloroprocaine vs saline, lidocaine vs saline), block level (all groups), gender (all groups), and incidence of back pain (all groups). Despite statistically significant differences between the groups, all individuals were young and of normal body habitus.

30–50 mL of 3% chloroprocaine. The rate of injection was 5 mL/min. Additional boluses of 10 mL were given at 10-min intervals until the sensory blockade extended to the fifth thoracic dermatome, as assessed by the absence of cold sensation with cutaneous application of an alcohol-soaked gauze pad. After achieving at least a T-5 blockade level, no further injections were given. The study of each subject required approximately 4 h. Because the first three subjects experienced back pain, we modified our technique in the last two subjects to include infiltration of the paraspinous muscles with 6 mL of 0.75% bupivacaine.

Data were analyzed using one-way analysis of variance and Student–Newman–Keuls test and are presented as mean ± SD. Differences were considered significant at $P < 0.05$.

Results

Four of the five volunteers given chloroprocaine developed severe back pain beginning at the time the sensory blockade level receded to approximately the T-10 dermatome. Each described the pain in a similar manner: it was severe, spasmodic, and localized to the lumbar region. On physical examination, the paraspinous muscles were not palpably tense. Changes in body position and local application of heat did not relieve the pain. Oral aspirin (650 mg) also provided minimal relief. None of the volunteers received narcotic analgesics. Only one subject had near complete relief of pain by the time he left our care (about 3 h after the final injection). The other three continued to experience intense pain for the rest of the day and evening and described it as more severe than any previously experienced. One of these three, a former college football player, found that this pain was far worse than that accompanying a broken ankle. On awakening the following morning, these three experienced only a slight soreness at the site of injection. The single volunteer in the chloroprocaine group who did not experience severe back pain was the lightest and shortest of the group but had received one of the largest anesthetic doses.

In the lidocaine group, one subject experienced mild, aching, back pain that lasted approximately 24 h. Subjects in the saline group experienced moderate to severe lumbar pressure sensations at the time of injection. The sensation resolved quickly after completion of the injection. None of the volunteers given lidocaine or saline experienced severe back pain after the study.

The physical characteristics of each study group, as well as the initial and total anesthetic volume administered and the resulting sensory blockade levels, are summarized in Table 1.

All subjects, except those given lidocaine and leg warming, shivered vigorously at times during the studies. The maximum decrease in tympanic membrane temperature in subjects given chloroprocaine was ~1.5°C, and ~0.75°C in those who received lidocaine without leg warming. Subjects given saline or lidocaine with leg warming remained normothermic.

Discussion

The high incidence of severe back pain in our volunteers after epidural administration of chloroprocaine was an unanticipated but striking finding. We chose chloroprocaine for the same reasons it is frequently used for outpatient anesthesia: rapid onset, short duration of action, and low intravenous toxicity. After the first three subjects experienced such distressing symptoms, we realized that the adverse effects may have resulted because we had not infiltrated the paraspinous muscles with local anesthetic (as we did in the other studies). Therefore, we infiltrated 6 mL of 0.75% bupivacaine into the paraspinous tissues of the remaining two volunteers. The fourth did not experience pain. However, infiltration did not prevent severe pain in the fifth subject.

Although the saline, lidocaine, and chloroprocaine groups differed significantly in age, weight, height, and male/female ratio, all volunteers were young, healthy, and had normal body habitus. Therefore, it is unlikely that the slight morphometric differences between groups are clinically relevant. Because we studied only a small number of subjects, we did not perform regression analysis to determine the importance of individual morphometric variables.

The lidocaine group received a smaller initial volume than the chloroprocaine group; however, the total volume of anesthetic administered did not differ significantly. Furthermore, subjects given saline received much greater initial and total volumes of injectate than those given chloroprocaine. It is unlikely that the high incidence of severe pain seen only in those receiving chloroprocaine was caused by the large volume of injectate per se.

It is also unlikely that the back pain in those who received chloroprocaine was related to hypothermia or shivering because six of the volunteers given lidocaine also became hypothermic and shivered, but experienced no pain. Moreover, back pain was absent in the saline group despite induction of vigorous shivering.

Volunteers were given no analgesic medications during the studies. Because they did not undergo surgical procedures, incisional pain was not present. Furthermore, every effort was made to minimize positional discomfort before the onset of sensory blockade. Thus, we avoided factors that might obscure the association between epidural chloroprocaine administration and back pain in the clinical setting.

In general, the reported incidence of back pain after epidural anesthesia for nonobstetrical surgery is low and similar to that after general anesthesia (~2%) (3). However, investigators have recently described an association between severe back pain and the use of chloroprocaine for epidural anesthesia (4,5). In a retrospective study of ambulatory surgery patients, Orkin and Bogetz found a 42% incidence of back pain after epidural anesthesia with chloroprocaine (4). Their patients described similar, spasmodic lower back pain that was unrelieved by local application of heat, massage, or changes in position. The pain was severe enough to bring some patients to tears. The investigators found back pain to be associated with larger volumes and doses of chloroprocaine.

Fibuch and Opper noted a 40% incidence of back pain after epidural chloroprocaine, and no localized paralumbar muscle pain after administration of other agents (5). Patients in their study received relatively small total volumes (30 ± 5 mL) of chloroprocaine.

Levy et al. reported a prospective study of patients undergoing arthroscopy during epidural anesthesia (6). Many patients reported some degree of back pain regardless of the anesthetic agent used, but those who received chloroprocaine had a higher incidence of moderate and severe back pain. All but one of their patients had onset of back pain after discharge from the postanesthesia recovery room, presumably well after recovery from sensory blockade. In contrast, the onset of back pain coincided with recovery from sensory blockade in our subjects and in the patients studied by Orkin and Fibuch and their associates (4,5).

An association between epidural chloroprocaine and severe back pain has not been reported in obstetrical patients. Back pain is common after delivery with or without epidural analgesia (i.e., 30%–40%) (7). Therefore, an association with a particular anesthetic agent is less likely to be noticed. Administration of epidural narcotics might further obscure a relationship between pain and anesthetic technique. Alternatively, the physiologic changes of pregnancy may in some way protect the parturient from developing this complication of epidural chloroprocaine.

Back pain may result from local irritation of muscle and soft tissues due to leakage or infiltration of the anesthetic solution along the needle track (6) (also Astra Pharmaceuticals. Dear Doctor Letter, December 1988). The high incidence of back pain in our subjects after receiving large volumes of chloroprocaine is consistent with this theory. Although relatively small volumes were used in the patients studied by Fibuch and Opper (5), they have since reported that chloroprocaine was used for skin and needle track infiltration (8). Although all local anesthetics have some degree of myotoxicity (9), the low pH (2.7–4.0) of chloroprocaine may irritate soft tissues to a greater extent than other local anesthetics (10).

Severe back pain attributed to epidural chloroprocaine was not reported before introduction of the ethylenediaminetetraacetic acid-containing Nesacaine-MPF formulation. Fibuch and Opper have postulated that chloroprocaine-associated back pain may be due to hypocalcemic tetany in paraspinous muscles due to the presence of disodium ethylenediaminetetraacetic acid in this preparation (5). Consistent with this possibility, a recent communication reported effective treatment of chloroprocaine-associated back pain by intravenous infusion of CaCl (11).

Interestingly, chloroprocaine has been reported to antagonize opiate analgesia (12,13). It is possible that antagonism of endogenous opioids at the spinal level may contribute to the severity of pain experienced by those affected with this complication.

In conclusion, we observed a striking pattern of severe, spasmodic lower back pain in four of five young, healthy volunteers who received chloroprocaine for epidural anesthesia. Severe back pain was not observed in 14 other volunteers given epidural lidocaine or saline in previous similar studies. Our findings are consistent with those reported in clinical studies. The absence of confounding factors, including surgical pain and opioid analgesia, may explain the higher incidence noted in our group of volunteers. The current evidence suggests that back pain is likely after epidural anesthesia with large volumes of chloroprocaine. Leakage into soft tissues around the catheter or the use of chloroprocaine for needle track infiltration is probably contributory, but does not explain the severity of pain. Until the mechanism of this unusual effect is better understood, we recommend that consideration be given to this potential complication before using chloroprocaine for epidural anesthesia.

References

1. Ponte J, Sessler DI. Effects of cold and warm epidural saline injections in volunteers. Br J Anaesth 1990;64:731–3.
2. Sessler DI, Ponte J. Shivering during epidural anesthesia. Anesthesiology 1990;72:816–21.
3. Lund PC. Peridural anesthesia: a review of 10,000 administrations. Acta Anaesthesiol Scand 1962;6:143–59.
4. Orkin FK, Bogetz MS. Back pain following uncomplicated epidural anesthesia with chloroprocaine. Anesthesiology 1989; 71:A716.
5. Fibuch EE, Opper SE. Back pain following epidurally administered Nesacaine-MPF. Anesth Analg 1989;69:113–5.
6. Levy L, Randel GI, Pandit SK. Does chloroprocaine (Nesacaine-MPF) for epidural anesthesia increase the incidence of backache? (letter). Anesthesiology 1989;71:476.
7. Grove LH. Backache, headache, and bladder dysfunction after delivery. Br J Anaesth 1973;45:1147–9.
8. Fibuch EE, Opper SE. Back pain after epidural Nesacaine-MPF (letter). Anesth Analg 1990;70:225–6.
9. Foster AH, Carlson BC. Myotoxicity of local anesthetics and regeneration of damaged muscle fibers. Anesth Analg 1980;58: 727–36.
10. Ackerman WE. Back pain after epidural Nesacaine-MPF (letter). Anesth Analg 1990;70:224–5.
11. Dirkes J. Treatment of Nesacaine-MPF-induced back pain with calcium chloride (letter). Anesth Analg 1990;70:463–4.
12. Kotelko DM, Thigpen JW, Shnider SM, Foutz SE, Rosen MA, Hughes SC. Postoperative epidural morphine analgesia after various local anesthetics. Anesthesiology 1983;59:A413.
13. Grice SC, Eisenach JC, Dewan DM. Labor analgesia with epidural bupivacaine plus fentanyl: enhancement with epinephrine and inhibition with 2-chloroprocaine. Anesthesiology 1990;72:623–8.

Spinal Anesthesia in a Patient With Friedreich's Ataxia

Keshav Kubal, MD, Shital K. Pasricha, MD, and Mukul Bhargava, MD

Key Words: COMPLICATIONS, FRIEDREICH'S ATAXIA. ANESTHETIC TECHNIQUES, SPINAL—Friedreich's ataxia.

Friedreich's ataxia is an inherited autosomal recessive disorder with degenerative changes localized chiefly in the spinocerebellar and pyramidal tracts with dorsal root ganglion atrophy. There is, therefore, mixed upper and lower motor neuron involvement, but the cerebellar signs usually predominate. The cerebellar signs typically include ataxia, dysarthria, and nystagmus combined with weakness, spasticity, and atrophy of muscles. Pes cavus and scoliosis almost always develop. There is significant cardiomyopathy in 10%–50% of these patients. There are only a few reports on anesthesia for patients with Friedreich's ataxia. We report what we believe to be the first case of spinal anesthesia in a patient with Friedreich's ataxia.

Case Report

A 31-yr-old gravida 1, para 0 woman weighing 35 kg, 137 cm in height, and 39 wk pregnant was scheduled for an elective cesarean section. She had a known history of Friedreich's ataxia since the age of 10 yr and had been unable to walk since age 14 yr. She had two siblings with the same disease, one of whom had cardiomyopathy; she, however, denied any cardiac symptoms.

When she was 27 yr old she had undergone a reconstruction of both feet for pes cavus deformity under spinal anesthesia (local anesthetic agent unknown) that had to be augmented later with general anesthesia because of the long duration of surgery. She volunteered that she "had a difficult time coming out of it." According to her, she had a "problem breathing" after general anesthesia. Probably she had some residual muscular weakness after extubation and had subjective feelings of difficulty in breathing. The anesthesia records from the previous hospital indicated succinylcholine had been used for intubation after precurarization with 1 mg metubine; no other relaxants had been utilized during the surgery. Anesthesia had been maintained on isoflurane, and the trachea had been extubated at the end of surgery without difficulty. There was no statement of delayed emergence or dyspnea, and there was no record of neuromuscular blockade monitoring.

During examination on this admission, the patient was found to be of small frame with contractures, severe scoliosis, and sitting in a wheelchair. She had moderate dysarthria with a slight general tremor. Cardiac auscultation and electrocardiogram were within normal limits. No further cardiac evaluation was done. Pulmonary function tests showed a severe restrictive lung defect as well as an obstructive air flow abnormality with suboptimal performance. Forced vital capacity (0.57 L) was 19% of predicted value, FEV_1/FVC (forced vital capacity) was 60% of predicted, and residual volume (0.77 L) was 144% of predicted. While breathing room air, her Sa_{O_2} was 97%, pH 7.41, P_{CO_2} 31, and Pa_{O_2} 92 with base excess of −4.0 mmol/L. Sodium citrate (0.3 mol/L) was administered orally (30 mL) 0.5 h before surgery.

In the operating room the patient was monitored with continuous electrocardiogram, blood pressure cuff, and pulse oximeter. A 1500-mL bolus of dextrose free electrolyte solution was given intravenously. Spinal anesthesia was administered in the lateral position using 6 mg tetracaine, 0.6 mL 10% dextrose, and 0.1 mg epinephrine injected in the L3-4 space through a 22-gauge spinal needle. A sensory level of T-4 was achieved. The patient was given 4 L/min oxygen via a nasal cannula. She needed two pillows on the operating table, which she normally used while lying supine. The uterus was tilted using a wedge under the right hip. No dyspnea or difficulty breathing was observed. A 2278-g baby was born with an Apgar score of 8 at 1 min and 9 at 5 min.

Received from the Department of Anesthesiology, New York Medical College, Valhalla, New York. Accepted for publication September 24, 1990.

Address correspondence to Dr. Pasricha, Department of Anesthesiology, New York Medical College, Valhalla, NY 10595.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Twenty units of oxytocin was administered in a 1-L intravenous infusion after the birth of the baby. No intraoperative sedation was given.

The patient had an uneventful postoperative course. Spinal anesthesia lasted about 150 min. She was discharged 5 days later from the hospital. A follow-up inquiry at 3 mo revealed that the patient was doing fine with no exacerbation of symptoms of her basic disease.

Discussion

There are very few case reports of anesthesia administered to patients with Friedreich's ataxia. There is one case report from Japan (1) in which a 47-kg boy with Friedreich's ataxia showed hyposensitivity to *d*-tubocurare, 3 mg of which produced apnea for 90 min when used with nitrous oxide, oxygen, and halothane. On the other hand, in another patient with Friedreich's ataxia, atracurium and *d*-tubocurare were given on two different occasions while the patient was monitored by the train-of-four twitch responses. Recovery was uneventful, and the patient was extubated at the end of the procedure (2). Epidural anesthesia for laparoscopic tubal ligation has also been given to a patient with this form of ataxia (3).

In our patient, technical difficulty owing to severe kyphoscoliosis made epidural anesthesia with the attendant chance of a "patchy" block with unblocked segments appear to be an unwise choice. Therefore, we decided to use spinal anesthesia. There was some concern with a regional anesthetic technique because of the theoretical possibility of exacerbation of the disease. Our case report and the previous report of the successful use of epidural anesthesia (2) suggest that a regional technique can be used safely. Continuous spinal anesthesia with incremental doses could have been another choice. Because of the possible abnormal response to succinylcholine and uncertainty about the duration of muscle paralysis after nondepolarizing muscle relaxants, general anesthesia should be used cautiously. The possibility of the need for prolonged mechanical ventilation because of our patient's poor lung function tests secondary to severe kyphoscoliosis also contributed to our choice of regional anesthesia instead of general anesthesia.

In patients with Friedreich's ataxia, when regional anesthesia is contraindicated, awake intubation followed by inhalation anesthesia may be an alternative anesthetic choice. If muscle relaxants are needed, small incremental doses should be used in association with neuromuscular blockade monitoring. The possibility of prolonged intubation should be kept in mind.

In summary, we described a case of Friedreich's ataxia in which spinal anesthesia was successfully used for cesarean section.

References

1. Kume M, Zin T, Oyama T. Anesthetic experience with a patient with Friedreich's ataxia—a case report. Jpn J Anesth 1976;25:877–80.
2. Bell CF, Kelly JM, Jones RE. Anesthesia for Friedreich's ataxia. Anesthesia 1986;41:296–301.
3. Alon E, Waespe W. Epidura Anaesthesie bei einer Patient mit Friedreichscher Ataxie. Reg Anaesth 1988;11:58–60.

ANESTH ANALG
1991;72:259–61

Myocardial Infarction Accompanying Acute Clonidine Withdrawal in a Patient Without a History of Ischemic Coronary Artery Disease

Keith H. Berge, MD, and William L. Lanier, MD

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—clonidine.

Clonidine is an antihypertensive drug, the mode of action of which is primarily via central nervous system α_2-agonist activity (1). Acute clonidine withdrawal has been reported to cause a hyperdynamic state (1). We describe a case of acute clonidine withdrawal that resulted in myocardial ischemia and probable infarction in a patient with no prior history of ischemic coronary artery disease. This represents, to the best of our knowledge, the first report of acute clonidine withdrawal resulting in myocardial infarction.

Case Report

The patient was a 67-yr-old white woman admitted to the hospital the evening before anticipated patch angioplasty of the right femoral artery. Past medical history was significant for claudication and multiple failed distal vascular bypass grafts. Translumbar aortography several days before admission revealed atheromatous disease of the abdominal aorta, right renal artery, and distal arteries bilaterally. Medical history included medically treated hypertension and hypothyroidism. Her only cardiac complaint was occasional palpitations. The patient specifically denied a history of angina or prior myocardial infarction. Chronic oral medications included levothyroxine sodium 0.1 mg; Dyazide (hydrochlorothiazide 50 mg and triamterene 100 mg), and potassium supplement (10 mEq) daily; captopril 25 mg, and isosorbide dinitrate 10 mg three times a day; and clonidine 0.4 mg twice a day.

Upon admission to the hospital on the evening before scheduled surgery, blood pressure (BP) was 170/90 mm Hg and heart rate (HR) was 85 beats/min. On the morning of surgery, BP had increased to 200/110 mm Hg and HR to 125 beats/min. Surgery was postponed, and the patient was transferred to an intensive care unit for preoperative BP control.

Upon admission to the intensive care unit at 8:00 AM, BP was 240/130 min Hg and HR was 110 beats/min. An intravenous sodium nitroprusside infusion was begun in an effort to control BP, and a radial artery catheter was placed for direct monitoring of BP. Sodium nitroprusside had only a minimal effect in controlling the BP. Shortly after initiation of sodium nitroprusside, a tachycardia with narrow QRS complexes at a rate of 170 beats/min developed, which 5 mg intravenous verapamil slowed to 150 beats/min. Shortly thereafter the patient complained of substernal pain, became diaphoretic, and vomited. An electrocardiogram obtained at 8:30 AM revealed approximately 1-mm ST-segment depression in leads V_1–V_3. The sodium nitroprusside infusion was discontinued simultaneous with initiation of sublingual and intravenous nitroglycerin therapy. In addition, intravenous labetalol was given in 5-mg increments to a total dose of 25 mg. Thereafter, HR decreased to 90 beats/min, BP declined to 170/90 mm Hg, and the patient's chest pain ceased. A review of the patient's records revealed that she had been chronically treated with clonidine. Upon admission to the hospital the previous evening, the patient was given nitropaste therapy as a replacement for her isosorbide dinitrate; however, she had not received her usual doses of either clonidine or captopril between hospital and intensive care unit admission. Hemodynamic stability was maintained with intravenous labetalol until resumption of oral clonidine and captopril could prevent a recurrence of the hyperdynamic state.

Received from the Department of Anesthesiology, Mayo Clinic and Mayo Medical School, Rochester, Minnesota. Accepted for publication October 4, 1990.

Address correspondence to Dr. Berge, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

The pending surgery was canceled. A subsequent electrocardiogram showed new precordial T-wave inversions that returned to normal over several days. Cardiac isoenzyme changes were suggestive of, but not diagnostic of, necrosis. This, along with the persistent electrocardiographic changes and the clinical presentation, led to the diagnosis of probable nontransmural anterior myocardial infarction. The patient was discharged 6 days later. Follow-up coronary angiography revealed a 70% occlusion of the left main coronary artery and a 50% occlusion of the right coronary artery. The patient underwent an uncomplicated three-vessel coronary artery bypass grafting procedure 7 mo later. This was followed 5 mo later by an uncomplicated aortobifemoral artery bypass graft procedure.

Discussion

Clonidine is not available for parenteral administration. Therefore, the perioperative period is the time when withdrawal is most likely, due to the usual practice of restricted oral intake. Since the first descriptions of the hyperdynamic response precipitated by acute clonidine withdrawal (2,3), there have been numerous case reports in the literature confirming the existence of this phenomonon (4–15). Although most of these episodes resolved without complication, at least one fatal outcome has been reported. This was a 51-yr-old man who died from an acute cerebellar hemorrhage that occurred during a hypertensive crisis precipitated by clonidine withdrawal (7).

The symptoms and signs of clonidine withdrawal develop within 12–24 h after the last dose of the drug. They consist of restlessness, insomnia, irritability, abdominal pain, nausea, and headache. Dramatic tachyarrythmias and hypertension resembling those seen with pheochromocytoma may develop (16). Urinary and arterial plasma catecholamine levels increase twofold to ninefold (4). Despite reports to the contrary (1,11), clonidine rebound hypertension may occur with discontinuation of daily doses as low as 0.1–0.4 mg (5,9,12,14,17). The hypertension is a true "overshoot," not merely a return to pretreatment BP (17). The frequency of this rebound after acute withdrawal is greater than 50% (16,18).

Clonidine probably exerts its antihypertensive effect by decreasing the sympathetic outflow from the vasoregulatory centers of the central nervous system (19). It exerts no antihypertensive effects in tetraplegics (20). The hemodynamic consequences include a decrease in HR (16) and in systolic and diastolic BP (1). Homeostatic cardiovascular reflexes are maintained, with the result that problems with orthostatic hypotension are avoided (1). Chronic use of clonidine may result in the "up-regulation" of postsynaptic α_1-adrenergic receptors, a feature shared with other drugs that decrease peripheral catecholamine stores or interfere with their action (e.g. β-adrenergic blocking drugs) (14,21). This up-regulation may be instrumental in the rebound hypertension seen with clonidine withdrawal, because the high levels of circulating catecholamines interact with a greatly increased pool of available receptors (21). Although the duration of clonidine therapy required to induce up-regulation, and therefore the risk associated with acute withdrawal, has not been elucidated, no rebound or overshoot occurred in patients on daily doses of 0.3 mg clonidine when the drug was abruptly withdrawn after 3 days of therapy (22).

The hypertension seen with clonidine withdrawal is exacerbated by preexisiting β-blockade (8,23). This is believed to result from an unopposed α-agonist effect causing increases in peripheral vascular resistance (8).

The best management of the hyperdynamic state produced by acute clonidine withdrawal is prevention. Care must be taken in directing patient drug intake during the admission process and in writing admitting orders for preoperative patients to insure that clonidine therapy will not be interrupted throughout the perioperative period. If a surgical procedure is likely to lead to intestinal ileus and failure to absorb enteral medicines, the need to provide clonidine by a nonenteral route must be anticipated. One option is a recently introduced transdermal clonidine patch. Both the transdermal (19) and the rectal (12) routes have proven effective in the perioperative period. The transdermal route requires 24–48 h to reach peak effect; rectal administration results in a response within 45 min.

Several different regimens have been proposed for treatment of the hyperdynamic state associated with acute clonidine withdrawal (1,13,14,24). Most consist of reinstitution of clonidine and include a combination of vasodilators (e.g., nitroprusside, hydralazine, phentolamine) and β-blocking agents. Labetalol, with combined α- and β-blocking properties, is also effective (14), and labetalol probably contributed to the restoration of normal cardiovascular function in the case we have presented.

Recommendations for the elective withdrawal of patients on chronic clonidine suggest that the dose should be decreased gradually over 7 or more days to prevent rebound (1). However, one case report described the onset of dramatic overshoot in BP and urinary catecholamines starting 10 days into a gradual withdrawal regimen, with mean systolic BP and urinary catecholamine levels peaking at days 14 and 15, respectively (6).

In summary, we present what we believe to be the first reported case of acute clonidine withdrawal resulting in myocardial infarction. This adverse outcome apparently resulted from the failure of the patient to receive her usual dose of oral clonidine, 0.4 mg twice a day, a dose less than that generally reported to be associated with risk from rebound symptoms upon acute withdrawal (1,11).

References

1. Stoelting RK. Pharmacology and physiology in anesthetic practice. Philadelphia: JB Lippincott, 1987:297–8.
2. Conolly ME. Catapres in hypertension. London: Butterworths, 1969:85–99.
3. Hokfelt B, Hedeland H, Dymling JF. Studies of catecholamines, renin and aldosterone following Catapresan (2-(2,6-dichlor-phenylamine)-2-imidazoline hydrochloride) in hypertensive patients. Eur J Pharmacol 1970;10:389–97.
4. Hansson L, Hunyor SN, Julius S, Hoobler SW. Blood pressure crisis following withdrawal of clonidine (Catapres, Catapresan), with special reference to arterial and urinary catecholamine levels, and suggestions for acute management. Am Heart J 1973;85:605–10.
5. Brodsky JB, Bravo JJ. Acute postoperative clonidine withdrawal syndrome. Anesthesiology 1976;44:519–20.
6. Vanholder R, Carpentier J, Schurgers M, Clements DL. Rebound phenomenon during gradual withdrawal of clonidine. Br Med J 1977;1:1138.
7. Vernon C, Sakula A. Fatal rebound hypertension after abrupt withdrawal of clonidine and propranolol. Br J Clin Pract 1979;33:112–21.
8. Bruce DL, Croley TF, Lee JS. Preoperative clonidine withdrawal syndrome. Anesthesiology 1979;51:90–2.
9. Stevens JE. Rebound hypertension during anaesthesia. Anaesthesia 1980;35:490–1.
10. Ferguson RP, Alvino E. Rebound hypertension after low dose clonidine withdrawal. South Med J 1983;76:98.
11. Van Der Geest S, Van Dijk RB, Donker JM. Clonidine withdrawal syndrome in a patient with heart failure. Crit Care Med 1985;13:444–5.
12. Johnston RV, Nicholas DA, Lawson NW, Wallfisch HK, Arens JF. The use of rectal clonidine in the perioperative period. Anesthesiology 1986;64:288–90.
13. Hauger-Klevene JH. Treatment of clonidine rebound syndrome with sublingual captopril. N Engl J Med 1986;314:181–2.
14. Mehta JL, Lopez LM. Rebound hypertension following abrupt cessation of clonidine and metoprolol. Arch Intern Med 1987; 147:389–90.
15. Stewart M, Burris JF. Rebound hypertension during initiation of transdermal clonidine. Drug Intell Clin Pharm 1988;22: 573–4.
16. Kosman ME. Evaluation of clonidine hydrochloride (Catapres). JAMA 1975;233:174–6.
17. Neusy AJ, Lowenstein J. Blood pressure and blood pressure variability following withdrawal of propranolol and clonidine. J Clin Pharmacol 1989;29:18–24.
18. Geyskes GG, Boer P, Dorhout Mees EJ. Clonidine withdrawal mechanism and frequency of rebound hypertension. Br J Clin Pharmacol 1979;7:55–62.
19. Reid JL. Central alpha-2 receptors and the regulation of blood pressure in humans. J Cardiovasc Pharmacol 1985;7:S45–50.
20. Reid JL, Wing LMH, Mathias CJ, Frankel HL, Neill E. The central hypotensive effect of clonidine. Clin Pharmacol Ther 1977;21:375–81.
21. Barash PG, Cullen BF, Stoelting RK. Clinical anesthesia. Philadelphia: JB Lippincott, 1989:181.
22. Planz G, Beckenbauer U, Bundschu HD. Response of plasma catecholamines and blood pressure to clonidine and to sudden withdrawal of the drug in subjects with essential hypertension. Int J Clin Pharmacol Ther Toxicol 1982;20:474–8.
23. Bailey RR. Rapid clonidine withdrawal. Br Med J 1976;1:942–3.
24. Campbell BC, Reid JL. Regimen for the control of blood pressure and symptoms during clonidine withdrawal. Int J Clin Pharm Res 1985;4:215–22.

Letters to the Editor

Prevention of Nitrous Oxide-Induced Increases in Endotracheal Tube Cuff Pressure

Key Words: ANESTHETICS, GASES–nitrous oxide. EQUIPMENT, CUFFS–endotracheal.

To the Editor:

Control of cuff pressure of endotracheal tubes during anesthesia seems to be an ongoing problem in the United States, as the recently published report of Resnikoff and Katz (1) shows. Far away, from the Old World over the ocean, where people are speaking and writing in languages that almost no American understands, please allow me to point out that this problem has been solved in Europe for at least 7 yr.

In 1983, in the German journal *Der Anaesthesist*, a paper was published entitled "The rediffusion system: limitation of nitrous oxide-induced increases of the pressure of endotracheal tube cuffs" (2). In that paper a new and simple system of limiting cuff pressures to a safe level of less than 25 mm Hg was described. The idea of the system was as follows.

As there is no possible safe way to exclude nitrous oxide diffusion into the cuff—all methods described in the literature have some limitations—the nitrous oxide, once it has diffused into the cuff, should be able to leave the "inflation system" (cuff, connecting tube, pilot balloon, inflation line) somehow. Thus the idea of solving the problem not with the cuff but with the pilot balloon presented itself. Because the cuff and the pilot balloon communicate via the connecting tube, an increase of the nitrous oxide concentration in the cuff will be accompanied by a similar increase of the nitrous oxide concentration in the pilot balloon. There is always a gas exchange between the cuff, at body temperature, and the pilot balloon, at room temperature, an exchange contributed to by the pump action of changing airway pressure during ventilation (3). So it should be possible that the nitrous oxide that has diffused into the air-filled inflation system, through the cuff wall, can diffuse into the room air via the wall of a suitable pilot balloon.

The above was the basis for the experiments to develop a "rediffusion system" (2). For the study of the rediffusion effect an ordinary high-volume, low-pressure cuff (Lanz 8.5-mm ID endotracheal tube cuff) was used. This cuff was combined with a "pilot balloon" larger in size and with a thinner wall than the cuff. The new inflation system was then inflated with air to a pressure of 15 mm Hg and the cuff exposed in an atmosphere of 66% nitrous oxide in oxygen. The system was connected to a pressure transducer (American Optical model 5145) and the pressure recorded continuously (Figure 1).

Within 6 h of in vitro conditions simulating those seen in clinical practice, the pressure increased to only about 25 mm Hg. These findings were confirmed with in vivo studies using the same experimental setup: the cuff pressure again reached a plateau of approximately 25 mm Hg after 150 min of anesthesia and then remained at this level.

Based on these in vitro and in vivo experiments an endotracheal tube with a "rediffusion system" for clinical use was developed. In 1985, Mallinckrodt Medical GmbH, Europe, started promoting a patent-protected endotracheal tube with that system European-wide (U.S. Patent No. 4407281, U.K. Patent No. 2080690 B, German Patent No. DE 3028568 C 2). Since that time the tube has been in clinical use several million times with excellent results (4) and without any problems.

In conclusion, the problem has already been solved, although documented mainly in German-language jour-

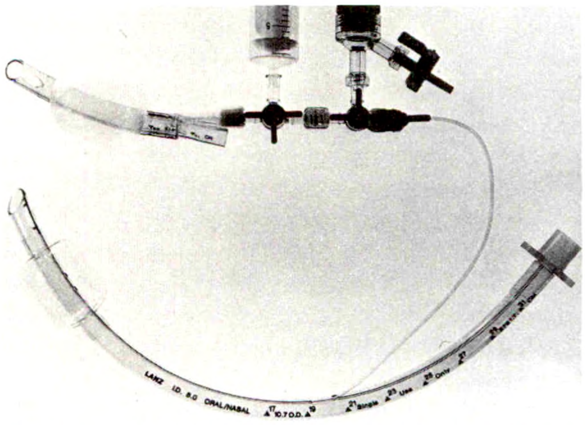


Figure 1. A model of the experimental "rediffusion system." The Lanz cuff was combined with a Mallinckrodt Hi-Lo cuff working as a pilot balloon. To the top of the picture the inflation syringe (*left*) and the pressure transducer (*right*) are to be seen (from Reference 2, with kind permission).

©1991 by the International Anesthesia Research Society

nals. A knowledge of languages is always beneficial, as we find when studying American journals.

L. Brandt, MD, PhD
Klinik fuer Anaesthesiologie
Johannes Gutenberg-Universitaet
Langenbeckstrasse 1
D-6500 Mainz 1
Germany

References

1. Resnikoff E, Katz JA. A modified epidural syringe as an endotracheal tube cuff pressure controlling device. Anesth Analg 1990;70:208–11.
2. Brandt L, Pokar H. The rediffusion system: limitation of ntirous oxide-induced increases of the pressure of endotracheal tube cuffs. Anaesthesist 1983;32:459–64.
3. Crawley BE, Cross DE. Tracheal cuffs. Anaesthesia 1975;30:4–11.
4. Lipp M, Brandt L, Daublaender M, Peter R, Baerz L. Frequency and extent of airway complaints following general anesthesia. Anaesthesist 1988;37:758–66.

Confirmation of Correct Endotracheal Tube Placement

Key Words: INTUBATION, TRACHEAL—complications, esophageal placement. EQUIPMENT, ESOPHAGEAL DETECTOR DEVICE.

To the Editor:

The report of Sosis and Sisamis (1) raises yet again the important topic of rapid and reliable detection of a misplaced endotracheal tube. Although their description is quite valid, it is also limited in its application in that oxygen desaturation does not precede all intubations. What is needed is a simple, rapid, and effective method for confirmation of tube placement, which can be used in all cases.

One simple piece of equipment that does not appear to have received much coverage in the American literature is the esophageal detector device described by Wee (2). This consists of a 60-mL syringe that is fitted, by way of an adaptor, over the end of a recently placed endotracheal tube. Because of the tracheal cartilage, air can be freely aspirated if the tube is correctly placed, whereas with an esophageal intubation the soft walls collapse, making aspiration of air difficult or impossible. Trials in over 100 patients correctly detected tube placement in all cases, the only equivocal result was given by a blocked tube, which needed replacement in any case. The device has subsequently been used routinely in 2000 patients, with equally good results (3). A modification has been described in which the syringe is replaced with a self-inflating bulb, which makes the device even simpler to use (4) while retaining the same reliability.

Ian Smith, FFARCS
Department of Anesthesia
Washington University
660 Euclid Avenue
St. Louis, MO 63110

References

1. Sosis MB, Sisamis J. Pulse oximetry in confirmation of correct tracheal tube placement (letter). Anesth Analg 1990;71:309–10.
2. Wee MYK. The oesophageal detector device. Anaesthesia 1988;43:27–9.
3. Wee MYK. Comments on the oesophageal detector device (letter). Anaesthesia 1989;44:930–1.
4. Williams KN, Nunn JF. The oesophageal detector device. Anaesthesia 1989;44:412–4.

Everything Old Is New Again

Key Words: ANESTHETIC TECHNIQUES, SPINAL, EPIDURAL—reversal.

To the Editor:

Reversal of epidural anesthesia by epidural saline injections as described by Johnson et al. (1) in many ways reaffirms reports of similar techniques used to shorten the duration of spinal anesthesia. Tuohy (2) described termination of spinal anesthesia ("in a short period") by irrigation of the subarachnoid space with physiologic saline solution, an idea he attributed to Lemmon. Koster et al. (3) showed that saline injection into the subarachnoid space reversed the motor paralysis seen after intrathecal procaine injection. Sargent et al. (4) successfully applied the same technique in dogs and found that flushing the subarachnoid space with saline achieved the greatest diminution of anesthesia if the elapsed time between local anesthesia injection and saline flush occurred before the anesthetic had a chance to "fix" (15–20 min for procaine, 30 min for tetracaine). Also, aspiration of cerebrospinal fluid has been shown to shorten the duration (or terminate) the anesthetic effect of several local anesthetics (5,6) and has been used to ameliorate the effects of intrathecal morphine overdose (7). Irrigation of the subarachnoid space has also been shown to be an effective treatment for accidental intrathecal injection of hypertonic contrast media (8).

Although irrigation of the subarachnoid space results in the deletion and removal of local anesthetics (etc.), epidural injection of crystalloid solutions may work in a somewhat different manner. Johnson et al. (1) hypothesize that epidural injections cause caudal and cranial spread of local anesthetic, diluting the concentration of drug in the epidural space. Thus, local anesthetics would tend to move from the cerebrospinal fluid down a concentration gradient into the epidural space away from its primary site of action. Other factors such as pH changes in the epidural space, as well as increases in the secretion and clearance of cerebrospinal fluid, both of which have been associated with injections into the epidural space, may also play a role in the alterations seen in epidural anesthesia. Regardless of their mechanism of action, these maneuvers may allow for an increased degree of control when neuraxial anesthesia is employed, making regional blocks (continuous spinal and continuous epidural anesthesia) more appealing to both patient and practitioner.

Brian K. Bevacqua, MD
William F. Cleary, MD
Anesthesia Service
Veterans Administration Medical Center
Cleveland, OH 44106

References

1. Johnson MD, Burger GA, Mushlin PS, Arthur GR, Datta S. Reversal of bupivacaine epidural anesthesia by intermittent epidural injections of crystalloid solution. Anesth Analg 1990;70:395–99.
2. Tuohy EB. Continuous spinal anesthesia: its usefulness and technique involved. Anesthesiology 1944;5:142–8.
3. Koster H, Shapiro A, Warshaw R, Margolick M. Removal of procaine from the cerebrospinal fluid during anesthesia. Arch Surg 1939;39:682–5.
4. Sargent WW, Bradley WE, Van Bergen FH. An electrophysiologic evaluation of the spinal fluid exchange technique in diminishing spinal anesthesia. Anesth Analg 1971;50:748–58.
5. Converse JG, Landmesser CM, Harmel MH. The concentration of pontocaine hydrochloride in the cerebrospinal fluid during spinal anesthesia and the influence of epinephrine in prolonging the sensory anesthetic effect. Anesthesiology 1954;15:1–10.
6. Garcia E. By-effects with spinal anesthesia and means to combat them. JAMA 1919;73:946.
7. Kaiser KG, Baiton CR. Treatment of intrathecal morphine overdose by aspiration of cerebrospinal fluid. Anesth Analg 1987;67:475–7.
8. Tartiere J, Gerard J, Peny J, Hurpe J, Quesnel J. Acute treatment after accidental intrathecal injection of hydrotonic contrast media. Anesthesiology 1989;71:169.

Neurally Evoked Compound Electromyogram in the Clinical Setting

Key Words: NEUROMUSCULAR TRANSMISSION, MEASUREMENT. MEASUREMENT TECHNIQUES, ELECTROMYOGRAPHY.

To the Editor:

I read with interest the nice case report documenting the occurrence of vancomycin enhancement of vecuronium-induced neuromuscular block as a clinical possibility (1). In reading Figure 1 of the paper, however, I noticed that the vertical scale, labeled "EMG responses," was up to 160 mV.

It is very unlikely for such a high EMG voltage to be evoked by stimulation of the ulnar nerve. Usual values are 0–25 mV. Could the patient's baseline response be 16 mV instead of 160 mV? Or shouldn't a time-integrated unit be used? Please kindly clarify for the literature.

Chingmuh Lee, MD
Department of Anesthesiology
Harbor-UCLA Medical Center
1000 West Carson Street
Torrance, CA 90509

Reference

1. Huang KC, Heise A, Shrader AK, Tsueda K. Vancomycin enhances the neuromuscular blockade of vecuronium. Anesth Analg 1990;71:194–6.

In Response:

We appreciate Dr. Lee's comments. It is possible that the figures we quoted were multiplied by some constant factor. However, we have not been able to verify this with the technical support staff at DATEX Instruments.

The EMG responses presented in our case report were obtained from the RS-232 serial port of NMT221. The NMT monitor sends out a three digit integer ranging from 0 to 255 for each sample from an eight-bit analogue to digital converter (A-D), which is preceded by a variable gain amplifier. When the supramaximal stimulus is found at less than 70 mA (220 V), the gain of the preamplifier is set to 20. According to the NMT221 service manual, the A-D input range is 0–4.7 V DC. This means that, with the gain set at 20, each step in A-D output is equal to 4.7/20/255 or 0.92 mV. The numbers we reported have not been corrected by the 0.92 factor, thus the baseline value of 160 mV is actually 147 mV.

After receiving Dr. Lee's comments we examined the analogue outputs at the back of NMT221 with a Tektronix 465 oscilloscope. The signals we observed are DC pulses in the 0–200-mV range. We believe that the figures we reported are correct so far as defined by DATEX Instruments of Helsinki, Finland, the manufacturer of NMT221. We do not know if these numbers are the actual raw EMG signals because we rely on NMT221 to separate EMG from stimulus artifacts. We regret any confusion this may have caused.

We believe that the importance of our report lies not in the absolute values of the evoked EMG voltages but in the relative changes that occurred.

K. C. Huang, MD
Department of Anesthesiology
Medical College of Virginia
Richmond, VA 23298

References

1. Huang KC, Heise A, Shrader AK, Tsueda K. Vancomycin enhances the neuromuscular blockade of vecuronium. Anesth Analg 1990;71:194–6.
2. NMT221 Service Manual, Puritan-Bennett Corporation. Wilmington, Mass. P/N 221016(A) 9/84.

Modification to an Anesthesia Breathing Circuit to Prolong Monitoring of Gases During the Use of Humidifiers

Key Words: EQUIPMENT, HUMIDIFIERS—problems with spectrometers. MONITORING, MASS SPECTROMETRY—moisture.

To the Editor:

Prolonged use of humidifiers in an anesthesia breathing circuit frequently results in inability to monitor ETco$_2$ and other gases because of accumulation of moisture in the

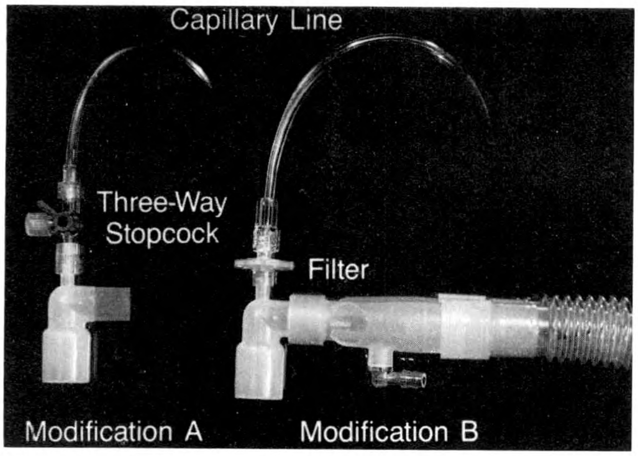


Figure 1. A three-way stopcock between the connecting port of the 90° elbow and the sampling capillary line; opening the three-way stopcock only when gas analysis is needed reduces the amount of moisture entering the sampling line (modification A). A 0.8-μm filter between the connecting port of the 90° elbow and the sampling line essentially prevents moisture from entering the sampling line (modification B).

sampling tubing that connects the sampling port to the gas analyzer. We frequently encounter this problem when using a Perkin-Elmer mass spectrometer. Monitoring of anesthetic gases, oxygen, and carbon dioxide could be prolonged by the interposition of a three-way stopcock between the gas sampling elbow (Dryden Corporation No. 16003) and the sampling capillary line, and opening the three-way stopcock only when gas analysis is needed (Figure 1, modification A). Although this modification did prolong the monitoring interval, it is time-consuming, impairs the surveillance effectiveness of an automatic sampling device to detect changes in gas concentrations, and still results in sampling line occlusion during prolonged surgical procedures. To maintain the surveillance capability of the mass spectrometer and to eliminate cumbersome and time-consuming use of a three-way stopcock, we inserted a 0.8-μm filter (i.e., a Marquette type 400148-001 disposable filter) between the connecting port of the 90° elbow and the sampling line (Figure 1, modification B). This isolates the sampling line from the direct influence of moisture from the anesthesia breathing circuit.

We observed the continuous monitoring time interval for a control group ($n = 6$) and a group with the in-line filter modification ($n = 6$). The time interval was measured from the start of humidification to the moment when the mass spectrometer noted "line blocked" or to the end of anesthesia. In the control group, useful monitoring time was 68 ± 22 min, whereas in the group with the in-line filter, useful monitoring time was 358 ± 36 min ($P < 0.001$ unpaired t-test). In three of the six patients in the group with modification B, the line remained unblocked during the entire surgical procedure (380, 405, and 420 min). In the other three patients, the filter was replaced when the "line blocked" warning was seen, after which monitoring with the mass spectrometer was successfully continued without replacing the sampling tubing.

Although this modification increases "proliferation complexity" of the anesthesia system (1), we think the benefit of enabling continuous gas analysis by mass spectrometry during surgery outweighs the disadvantages of the system.

Juraj Sprung, MD, PhD
Eugene Y. Cheng, MD
Department of Anesthesiology
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, Wisconsin 53226

Reference

1. Gaba DM, Maxwell M, DeAnda A. Anesthetic mishaps: breaking the chain of accident evolution. Anesthesiology 1987;66:670–6.

Endobronchial Cuff Pressures of Double-Lumen Tubes

Key Words: EQUIPMENT, TUBE—endobronchial. ANESTHETIC TECHNIQUES, ENDOBRONCHIAL.

To the Editor:

The paper by Brodsky et al. (1) that compared cuff pressures in bronchial cuffs of four types of double-lumen tube focused on cuff pressure when a gas-tight seal was achieved in a model bronchus, and on its relationship to cuff volume under this condition. The justified implication throughout is that inflation of the cuff beyond this volume and pressure causes an increase in cuff pressure that can cause endobronchial damage.

Such damage is likely to be caused by pressure on the bronchial wall from the cuff. Depending on the visoelastic properties of the material of which the cuff is made, the relationship between intracuff pressure and cuff volume is likely to vary. For example, the old red rubber high pressure/low volume cuffs may have higher intracuff pressures for a given cuff volume than an equivalent low pressure/high volume cuff. However, the resulting high circumferential mechanical stress in the cuff wall (2) means that less intracuff pressure is transmitted to the endobronchial wall. This is illustrated by Figure 1, which is taken from the work of Black and Seegobin (3) for cuffs on endotracheal tubes, using a model trachea in which "wall pressure" could be directly measured.

In algebraic terms, a relationship of the form Pic = Ptw + Pf(V,S) was suggested (4), where Pic is intracuff pressure, Ptw is tracheal wall pressure, and Pf(V,S) is a pressure contribution related to a function of cuff volume and stiffness.

Such a relationship can be derived, considering the cuff as a thin-walled pressure vessel (2), with some modifications and assumptions, and can be described as:

$$\mathrm{Pic} = \mathrm{Ptw} + \mathrm{Pic}\ (\text{in air}) \times f(r_1, r_2, t, \sigma_1, \sigma_2),$$

where Pic (in air) is intracuff pressure with the cuff suspended in air, and $f(r_1, r_2, t, \sigma_1, \sigma_2)$ is a mathematical

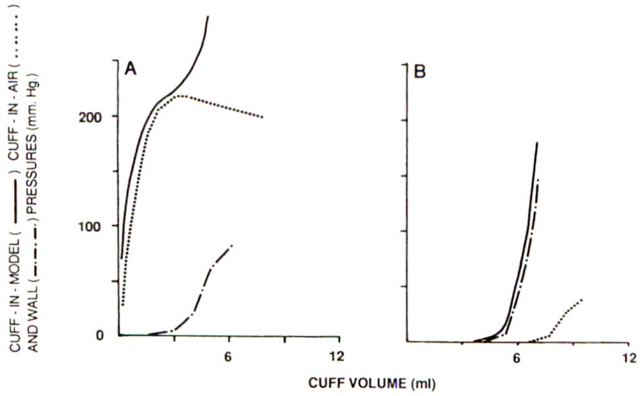


Figure 1. Pressure-volume relationships for low residual volume cuff (**A**) and high residual volume cuff (**B**). Cuff in air relationship (....), cuff in model relationship (————), and wall pressure (–·–·–). Reproduced from Black AMS and Seegobin RD, Anaesthesia 1981;36:498–511, with permission.

function of cuff radii of curvature (r_1, r_2), cuff thickness (t), and cuff principal circumferential mechanical stresses (σ_1, σ_2). In view of the time and temperature dependence of cuff material, it is difficult to determine a more exact relationship, even experimentally (personal communication, Portex Ltd., Hythe, Kent, U.K.). The relationship of the form

$$\text{Pic} = \text{Ptw} + \text{Pic (in air)},$$

as suggested by Homi et al. (5), has not been substantiated (3).

Brodsky et al. demonstrates a relationship between cuff volume and intracuff pressure, but the concept of bronchial wall pressure and its variable relationship to cuff volume and intracuff pressure is omitted, which may be misleading to readers.

Patrick T. Magee, MBBS, FFARCS
Department of Anesthesiology
University of Virginia
Charlottesville, VA 22908

References

1. Brodsky JB, Adkins MO, Gaba DM. Bronchial cuff pressures of double lumen tubes. Anesth Analg 1989;69:608–10.
2. Timoshenko S. Strength of materials. 3rd ed. New York: Van Nostrand Reinhold, 1976:117–9.
3. Black AMS, Seegobin RD. Pressures on endotracheal tube cuffs. Anaesthesia 1981;36:498–511.
4. Crawley BE, Cross DE. Tracheal cuffs: a review and dynamic pressure study. Anaesthesia 1975;30:4–11.
5. Homi J, Notcutt W, Jones JJ, Sparke BR. A method for comparing endotracheal cuffs: a controlled study of tracheal trauma in dogs. Br J Anaesth 1978;50:435–45.

In Response:

Dr. Magee's letter makes an interesting and useful point: the pressure transmitted to the bronchial wall is less than the pressure inside the cuff by an amount related to the pressure needed to maintain the inflation of the cuff itself. As mentioned, this factor is difficult to calculate or to measure experimentally, although the formula given, which considers the inflation factor to be equal to the pressure of the cuff when inflated while surrounded by air, may at least give a rough estimate of the actual wall pressure. The inflation factor is likely to be much higher for a "high pressure/low volume" cuff than for the "low pressure/high volume" cuff. Within each class of cuffs this factor is likely to be similar, although different cuff materials and geometries may cause some variation. Thus comparison of different "low pressure/high volume" cuffs is appropriate.

We agree with Dr. Magee that the wall pressure is the relevant variable, but we emphasize that when double-lumen tubes are properly used it is the wall pressure at *occlusion of the bronchus* that counts. Our study demonstrated that occlusion occurred at small *volumes* and *pressures* when some of the low pressure/"*high volume*" cuffs were used. The actual wall stress imparted by these cuffs is unknown, but in any case it can only be less than or equal to the cuff pressure itself. A further issue relates to the match between tube size and bronchus size because a mismatch will result in occlusion at an atypical volume and pressure. The effects of such a mismatch have not been investigated.

Finally, we point out that the actual contribution of bronchial cuff pressure/volume relationships to morbidity can only be made by studying animal models in which the integrity of the bronchial mucosa and wall can be assessed.

David M. Gaba, MD
Department of Anesthesia
Stanford University School of Medicine
Veterans Administration Medical Center
3801 Mirand Avenue
Palo Alto, CA 94304

Reuse of a Disposable Stylet With Life-Threatening Complications

Key Words: EQUIPMENT, DISPOSABLE—reuse.

To the Editor:

Karis recently suggested the advantages of reusing disposable single-use devices (1). Although I am a family practitioner, the letter came to my attention because of its relevance to the startling course of one of my patients. This 72-yr-old woman entered initially for elective foot surgery only to develop life-threatening complications from a reused disposable device.

My patient underwent bilateral foot surgery in early 1990. A difficult endotracheal intubation was performed after initial inadvertent esophageal intubation. On entering the esophagus, a 10-cm section of a Mallinckrodt Satin-Slip 14F aluminum stylet with plastic sheath broke off in the esophagus. This was not detected at the time.

Postoperatively her course was initially uneventful, but after a few days she began to have vague gastrointestinal symptoms and developed a low-grade fever. Although she had an extensive diagnostic workup over the next few weeks, no definitive diagnosis was made. Eventually, however, she presented with an acute abdomen. Emergency laparotomy revealed peritonitis with the 10-cm fragment of the broken stylet perforating the duodenum.

The following should be noted in this case:

(a) The stylet used here was aluminum (Mallinckrodt and Portex manufacture aluminum stylets), which is a brittle metal to begin with and more likely to break with reuse. The manufacturer cautions against reuse, citing the breakage hazard on the package.

(b) Upon examination several bends indicating reuse were observable in the 10-cm fragment of the broken stylet.

In view of this experience, Dr. Karis' position on reuse of disposable single-use devices appears too cavalier. Although one is tempted to hold that manufacturers promote one-time use from a strictly economic standpoint, safety factors and the high cost of product liability insurance sustained by the manufacturers must be considered.

Transmission of infection and chemical irritation from traces of sterilizing solutions and gases are known risks of reusing single-use devices. In addition, malfunction (for example, most intubating stylets lose their malleability with reuse) and weakening with the tendency for failure and breakage need to be considered when one-time use equipment is reused.

One cannot estimate what reuse and resterilization of single-use devices can do to their integrity because of the impossibility of standardizing and enforcing reuse criteria. Certainly the patient should not be exposed to the risks of reuse of single-use devices especially when reuse involves a very small fraction of overall health costs. We can ill afford to be penny wise and pound foolish, in the best interests of patient care, when it comes to the issue of disposables.

Ritchard L. Fishman, MD
9505 East Telegraph Road
Pico Rivera, CA 90660

Reference

1. Karis JH. Hidden costs of disposables: is color coding desirable? Anesth Analg 1990;71:203–4.

The Burden of Progress: A Fable

Key Words: COMPLICATIONS, ANESTHETIC, MORTALITY AND MORBIDITY

To the Editor:

Dr. Arthur Keats' article on anesthetic mortality (1) deserves serious consideration. I cannot fault his logic, nor can I argue his points with scientific counterpoints. Yet I am troubled by what he has to say. Had our forefathers in 1846 embraced his gloomy outlook, they might have concluded that the introduction of anesthesia should be halted because not only did it render surgical care more expensive, it also spawned new mechanisms of maiming and killing surgical patients. I am sure that Dr. Keats would not want us to draw such conclusions. I accept his message as an attempt to provoke us to examine every dogma that comes our way. But we have to be careful not to exchange the dogmas he decries for the alternate dogma that no innovation can be accepted without scientific proof of its value. To make that point, I offer the following fable.

The Burden of Progress

> Now comes the pain of truth, to whom 'tis pain;
> O folly! for to bear all naked truths,
> And to envisage circumstance, all calm,
> That is the top of sovereignty.
>
> —John Keats

I was reading an article on the burden of progress as I flew to Atlanta, where I was to change planes to fly to Chicago. It never came to that.

Despite a layer of dense clouds at the Atlanta airport, the plane made a smooth, precise landing. As I disembarked, the captain stood at the door of the cockpit to greet the passengers. I stopped and asked, "How could you find the airport in such soup? Surely not by looking at a road map!" He smiled and waved me into the cockpit to show me his instruments.

My heart sank. Having just read about the burden of progress, I asked: "Do these instruments ever mislead you? What are the sensitivity and specificity of the instruments? Do they ever fail? There are so many of them (it was a DC 9-31), won't they confuse and distract you?"

He sighed and said, "Nothing is perfect. Yes, there are examples where pilots have been distracted by irrelevant data or wrong reports. But that is rare. And we do have back-ups. Here, for example, is our magnetic compass. It needs electricity only for illumination and works even during power failure." "I am glad, " I said, "that you still have such an old, proven, reliable, time-honored instrument as a back-up. Do you use it often? And if so, why bother with all those fickle electronic things in the first place?" "Well, I'll tell you," he said, "I haven't flown by that magnetic compass in years. We are required to have one on board, but we don't use it. For example, here in Atlanta Stone Mountain has a magnetic core that worries our old-fashioned compass!"

By then the last passenger had left the plane. The captain said he was going off duty and, before flying as a passenger to Chicago, had time to chat. So did I. We sat in a lounge and he told me how advance after technical advance over the years had transformed the cockpit of commercial and even private aircraft. He said, "Every instrument is designed to fill a gap left by the limitations of human physiology or performance."

"In anesthesia it is similar, " I said, "but it seems that every advance has brought us new complications. We may eliminate the dilemma of unrecognized esophageal intubation, only to replace it with the predicament of having a workplace so complex that only the nimblest can manage to escape the distractions that result from so much technological advancement."

"Are you telling me that anesthesia is no safer, and perhaps less safe today, than it was, say, 30 years ago?" he asked, obviously troubled by what he was hearing. I nodded, "That, indeed, is what some of our brightest professors are saying. How is that problem handled in aviation? Do you have evidence that all your fancy instruments have improved safety?" "Oh, but they have," he responded. "After piloting for 30 years, there is no doubt in my mind about that."

"That's what many of my colleagues say about safety in anesthesia too," I went on. "But clinical impressions [I drew down the corners of my mouth to show my disdain for such unscientific opinions] should not be confused with science. [Here I raised my eyebrows to give weight to the statement.] Scientific methods call for properly conducted, prospective studies, double-blinded, controlled, and statistically sound. Surely you have such investigations documenting, for example, the role of the magnetic compass in crashes or navigational errors such as when a captain wanted to fly to Orlando, but wound up in Tampa?"

He could not recall such studies. And as we talked it became apparent that he knew of no scientific experiment documenting the value of any of the high-tech devices that he used when piloting his aircraft. He kept saying, "Come on, if something is eminently reasonable, intuitively obvious, in harmony with the experience of uncounted colleagues, endorsed by experts, doesn't that count for something?"

I could not let him get away with such unscientific and clearly emotionally sustained statements. "How often has mankind been fooled by opinions, however noble; by dogma, however obvious; by experts, however experienced; or by prejudice, however hoary? No, no, only science can lead the way. We must not accept developments just because they make sense, just because they appear reasonable, just because they seem to fill a void, answer a need, or alleviate a difficulty."

He looked troubled and ordered a gin and tonic. I asked for a Shirley Temple. Then he said: "But is it not true that the instruments can help us to avoid human errors? For example, even small, single-engine planes—I hate them—have stall warnings. Is it not better to be warned before you find yourself in a spin that you may not be able to control?"

"You are falling into the trap set by every salesman who ever peddled an instrument," I said. "Assume that you install a new warning system that really works—that simply means that you will commit an error elsewhere, maybe even worse than the one you were trying to avoid. You are simply shifting errors from one plane, so to speak, to another. It is as if you have an allotment of human errors that you are destined to commit." Well, that was an exaggeration, but in the spirit of the moment.

He ordered another gin—hold the tonic—and said: "That's awful. Do you think that would be true for other innovations as well?" What a frightening idea! I could not remember having read scientific studies demonstrating the cost-to-benefit ratios for electric light or toasters. But I knew of people who had been electrocuted (accidentally and otherwise), or of children who had burned themselves on a toaster. We began to explore other illustrations of the same phenomenon, which we called Pandora's Paradigm: If a new thing is not scientifically proven to be better than an old thing, it will cause new problems that are as bad or worse than the old ones; from which it follows that any betterment linked to unproven new things is likely to be but a cruel deception.

We set out to test—admittedly unscientifically—the validity of Pandora's Paradigm by collecting examples with which we were familiar. He generated a list of new things related to transportation, starting with jet planes and going back to cars and horses and finally to shoes. I developed a list for anesthesia and retraced the evolution of the latest machine with bells and whistles and computerized monitors back to the Schimmelbusch mask and the lace handkerchief. There was no end to our lists of so-called advances that had found general acceptance without the benefit of scientific proof of their worth. We recorded our findings on paper napkins and soon had stacks of them; the waitress started eyeing us with suspicion.

Finally we got up. He shook his head and said: "I will not fly again. It is sheer folly to do so. We haven't even proven scientifically that planes without propellers can fly." Well, if an experienced pilot came to that conclusion, I was certainly not going to fly either.

We started walking toward Chicago.

It is a flaw
In happiness, to see beyond our bourn,—
It forces us in summer skies to mourn,
It spoils the singing of the nightingale.
—John Keats

J. S. Gravenstein, MD
Department of Anesthesiology
University of Florida College of Medicine
Gainesville, FL 32610-0254

Reference

1. Keats AS. Anesthesia mortality in perspective. Anesth Analg 1990;71: 113–9.

Anesthesia Mortality in Perspective

Key Words: COMPLICATIONS, ANESTHETIC MORTALITY AND MORBIDITY.

To the Editor:

The recent paper by Dr. Keats raises some very interesting points concerning anesthesia mortality (1). Although I am in complete agreement with what seems to be his main point, i.e., more well-defined studies aimed at defining the role of anesthesia in surgical mortality need to be undertaken, I find it debatable that there is no evidence that anesthesia mortality is improving.

No doubt comparing mortality studies done in Europe 10 yr ago with anesthetic mortality today in the United States is difficult. One could argue, however, given the current standard of anesthetic care in the United States, that anesthetic mortality may be even less than 1 per 10,000 as reported in these studies. At least one investigation performed in this country on anesthetic mortality covering the years 1969–1984 reported an incidence of anesthetic deaths of 0.9 per 10,000 (2).

Dr. Keats fails to mention one monitor that has almost certainly contributed to an improvement in anesthetic mortality over the last 40 yr; that is, the in-line oxygen analyzer. I will agree that there is no scientific evidence (studies) to support the premise that their routine use has led to a decrease in anesthetic-related deaths. The literature is replete with calls for routine use of these monitors for safety reasons (3,4). In addition, there are reports of intraoperative deaths secondary to delivery of hypoxic gas mixtures to patients that could have been prevented if oxygen analyzers had been used (5). It follows, then, that everything else being equal, anesthesia mortality has improved just from the routine use of oxygen analyzers.

Moreover, taken individually, Dr. Keats' points about anesthetic monitors may be true. From a practical (clinical) viewpoint, however, these monitors are almost always used in combination. Therefore, any individual limitation of one monitor may be quickly checked by another. In the example given to admonish the use of the "treacherous" automated blood pressure recorder, I will agree that if this were the only monitor used on this patient, then perhaps a bad outcome would follow. The concomitant use of a pulse oximeter (no pulse wave), esophageal stethoscope (blunted or absent heart sounds), and capnography (decreased $ETco_2$) would almost surely have to lead to an accurate diagnosis and timely intervention.

My point is that in spite of the lack of evidence, the routine use of these monitors in conjunction with a vigilant anesthesia practitioner almost certainly has led to a decrease in anesthesia mortality when compared with the time of the Beecher–Todd study. True, we are anesthetizing more seriously ill patients for more complex procedures, but we are much better equipped to do so.

Regarding the routine use of scavenging systems, there are inherent risks associated with their use, but I for one do not need to see the results of scientific studies to know that being exposed to even trace amounts of anesthetic gases on a daily basis cannot be of benefit to anyone.

In summary, although Dr. Keats makes many valid points in his editorial, I believe he is wrong in stating that anesthesia mortality is not on the decline. With the routine use of modern anesthesia monitors, oxygen analyzers, new and improved drugs, in combination with well-trained, vigilant anesthesiologists, anesthesia mortality must be improving. . . . The studies will follow.

Robert D. Culling, DO
Lovelace Medical Center
Albuquerque, NM 87108

References

1. Keats AS. Anesthesia mortality in perspective. Anesth Analg 1990;71:113–9.
2. Keenan RL, Boyan P. Cardiac arrest due to anesthesia. JAMA 1985;253:2373–7.
3. Marks WE. A plea for routine use of oxygen analyzers. Anesthesiology 1983;59:159.
4. Dorsch SE, Dorsch JA. Use of oxygen analyzers should be mandatory. Anesthesiology 1983;59:161–2.
5. Mazze RI. Therapeutic misadventures with oxygen delivery systems: the need for continuous in-line oxygen monitors. Anesth Analg 1972;51:787–92.

To the Editor:

I read with great interest the transcript of the T. H. Seldon Distinguished Lecture presented at the 64th Congress of the International Anesthesia Research Society by Dr. A. Keats (1). I too, share his interest in anesthesia-related mortality. There is no question that the literature on this issue is sparse at best. It is also true that we, as a specialty, have no clear definition of what constitutes an anesthetic death or how to identify one. I believe all medical specialties would be hard pressed to identify a clear cause of death when multiple interventions are introduced. I applaud Dr. Keats' call for scientific investigation of the rate of anesthetic mortality and, as a corollary, for an agreed upon definition of the same.

Unfortunately, I do not agree with his criticism of recent advances in our field, particularly monitoring advances. The suggestion that we should "use the oximeter to measure heart rate and get rid of the ECG" is shocking! I wonder how Dr. Keats would proceed if faced with a pulseless "healthy patient" during an anesthetic. Is the patient in ventricular fibrillation, asystole, third-degree heart block, or merely so hypovolemic (we don't want to produce water intoxication) that the pulse is no longer palpable? What occurred before the event? What is the appropriate therapeutic intervention without a diagnosis?

If we use an oximeter to monitor heart rate, does Dr. Keats suggest that we ignore the patients' oxygen saturation until it reaches a level of scientifically proven dangerous hypoxemia in order to avoid a "subpopulation . . . walking around without their front teeth"? Possibly, it would be more prudent to intervene while the oxygen saturation is decreasing but before a pathophysiologic manifestation of hypoxemia.

There will always be risks and benefits associated with the introduction of new anesthetic techniques or technology, including a learning curve associated with each innovation. As in all specialties we will always be faced with practitioners who do not perform at acceptable levels. One does not damn a new drug or device because it is not used in an appropriate manner. Is Dr. Keats asking for us to return to the days of open-drop ether, no intravenous access, finger on the pulse, no electric cautery, . . . until it is proven that each change is associated with improved patient outcome on a national scale?

Dr. Keats lecture has been published under the heading of Scientific Articles, but sounds more like a reminiscence for the "good old days, when times were simple." The industrial revolution had the Luddites smashing looms. I trust we do not attempt to repeat history.

John P. Abenstein, MSEE, MD
Department of Anesthesiology
Mayo Clinic
Rochester, MN 55905

Reference

1. Keats AS. Anesthesia mortality in perspective. Anesth Analg 1990;71: 113–9.

Endotracheal Tube Cuff Failure Due to Valve Damage

Key Words: EQUIPMENT, CUFFS—endotracheal tube.

To the Editor:

It is the practice among some anesthesia residents at our institution to store an air-filled syringe in the valve assembly of the endotracheal tube to assure syringe availability and maximize speed of cuff inflation after endotracheal intubation (Figure 1). We have experienced several instances of endotracheal tube cuff failure attributable to this practice. The mechanism of failure is the development of a crack in the hard plastic shell of the valve housing that renders the valve incompetent (Figure 1, inset). Whether this cracking is due to prolonged deformation stress by the syringe tip, excessive force used to seat a syringe intended for prolonged storage, or some other cause is not clear. Because injected air rapidly leaks through the cracked housing wall, it may prove impossible to inflate the endotracheal tube cuff without complete bypass of the valve assembly. This can be accomplished by cutting off the pilot balloon and inserting a 22-gauge intravenous catheter into the cut end of the connecting tubing (1). A three-way stopcock placed in the injection port of the intravenous catheter would serve as a substitute valve.

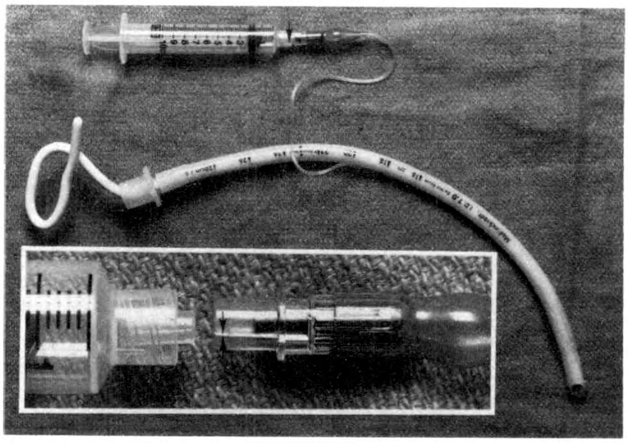


Figure 1. Endotracheal tube with syringe stored in valve assembly. Inset: Close-up view of valve demonstrating longitudinal crack (*arrows*) in valve housing.

The package insert provided by the manufacturer of our endotracheal tubes (Mallinckrodt Critical Care, Glens Falls, N.Y.) warns against possible cuff failure secondary to prolonged insertion of syringes or other devices in the valve assembly. Informal polling of members of our department suggests that this warning is not common knowledge. We add our recommendation against the practice to that of the manufacturer, especially in endotracheal tubes intended for emergency use where cuff failure may have serious consequences.

John E. Heusner, MD
Christopher M. Viscomi, MD
Department of Anesthesiology
University of Utah Medical Center
50 North Medical Drive
Salt Lake City, UT 84132

Reference

1. Watson E, Harris MM. Leaking endotracheal tube. Chest 1989;95:709.

Book Reviews

The Management of Pain, 2nd ed.

J. J. Bonica, J. D. Loeser, C. R. Chapman, and W. E. Fordyce, eds. Philadelphia: Lea & Febiger, 1990, 2120 pp (2 volumes), $225.00.

There has been a tremendous surge in the publication of pain-related books coincident with the emergence of pain management as an important subspecialty of anesthesiology. The most recently published books on the subject of pain management are loosely edited compendia of procedural methods designed to enhance profit, prestige, and ease of practice. The second edition of Bonica's *The Management of Pain* has appeared just when the question: "Which book should I buy?" was becoming a complex issue. The question is now easily answered.

Bonica is the "father" of modern pain management: he pioneered the therapeutic role of the physician anesthesiologist within a multidisciplinary setting. The first edition of this book in 1953 was the single most authoritative text on pain management but is no longer available. None of the tomes printed between editions presented as cohesive or comprehensive view of the field. Instead, the number and variety of new publications in the field serves as a reminder of the complex and individualized nature of pain practice and management. The second edition is even more comprehensive with added expertise gained through editorial collaboration with colleagues in neurosurgery, psychiatry, and rehabilitative medicine.

This reviewer suggests that this book be required reading for all residents training in anesthesiology as well as for medical students during their third and fourth years of medical school. For, regardless of specialty chosen, pain is a part of most disease processes. Certainly pain is the symptom that most often brings patients to medical attention. The ability to understand pain and to use its characteristics as an aid in diagnosis and treatment can only improve our acumen as doctors.

Dr. Bonica had as his mission the creation of a second "biblical" text of pain management. He has expanded the format and contents in keeping with advances fostered through a concerted multidisciplinary approach to pain diagnosis and therapy that began after publication of his first edition. He and his collaborators have created a two-volume cohesive, comprehensive textbook that carries the reader through history, across modalities, between diagnoses, and finally into a systems-oriented review of painful disorders and their palliation. Everywhere there are reminders that we are neither the first nor the only ones to have been stumped by a given problem or condition. This reviewer hopes that this book does not go out of print for a long time to come.

Wilhelmina C. Korevaar, MD
Department of Anesthesia
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Anesthesia for Cardiac Surgery

J. A. DiNardo and M. J. Schwartz, eds. Norwalk, Conn.: Appleton & Lange, 1990, 335 pp, $55.00.

Anesthesia for Cardiac Surgery is an excellent introductory text that should be required reading for the resident entering the cardiac operating room or the attending physician reentering this complex and growing field. The teacher of cardiac anesthesia will also find the textbook material presented in a manner that can serve as a model for teaching an organized basic course in cardiac anesthesia.

The book is well organized and formatted in its entirety as it proceeds from preparation of the patient to transport to the intensive care unit and postoperative care. Each chapter follows an organized pattern of the review of relevant physiology, outlines the specific goals of anesthetic care, and follows this plan through to the perioperative period. The authors through careful editing have achieved a work remarkable for its simplicity and comprehensiveness. Each chapter is understandable and coherent in isolation and as a part of the entire work.

The section of this textbook devoted to the preoperative preparation of the cardiac surgical patient is its strongest point. The first two chapters present an easily understandable, accurate review of the ever-increasing array of comprehensive preoperative screening examinations performed on patients about to undergo cardiac surgery. The section of Chapter 1 on cardiovascular evaluation presents excellent, concise explanations of stress testing, myocardial perfusion scintigraphy, echocardiography, and nuclear imaging, providing the reader with a basic understanding of these techniques in the context of their relevance to the perioperative period. Chapter 2, "Interpreting Cardiac Catheterization Data," in particular is invaluable to the

©1991 by the International Anesthesia Research Society

student of cardiac anesthesia as it provides a basic framework for this interpretation not to be found presented as elegantly elsewhere.

The midsection of this text—the chapters on monitoring, anesthesia for coronary surgery, congenital heart disease, valvular heart disease, emergency cardiac surgery, and pericardial disease—are well written and up to date. In general, they tend to be somewhat limited to the methods and techniques used at the Beth Israel Hospital in Boston. Although accurate and certainly acceptable as a method of perioperative care, a broad-based introduction to other methods would improve the usefulness of this part of the text.

The chapters on cardiopulmonary bypass, myocardial preservation, neurological injury, and postoperative care are another strong point of this textbook. They are comprehensive and well referenced. The material—which is in general fairly technical—has been well illustrated and organized. The recognition that comprehension of this material is important to building a working relationship with perfusionists, surgeons, and intensivists is a valuable part of the cardiac anesthesiologist's education.

The value and longevity of this book as an up-to-date clinical text would have been enhanced by the inclusion of material on four topics that are omitted: (a) pacemakers, (b) electrophysiology and automatic implantable cardiovertor-defibrillators, (c) cardiac transplantation, and (d) ventricular assist devices. Over the past decade, all of these areas have changed in the sophistication of their technology. The rapid increase in the number of patients undergoing both AICD implantation and cardiac transplantation is a fact that cannot be ignored. A concise chapter on these new developments would have improved the book.

In general, this concise text is an excellent starting point for the student of cardiac anesthesia and an excellent reference for the teacher of cardiac anesthesia. It deserves a place in the library of all participating in this field.

Ellise S. Delphin, MD
Columbia-Presbyterian Medical Center
Department of Anesthesiology
New York, New York

Scientific Foundations of Anaesthesia. The Basis of Intensive Care

Cyril Scurr, Stanley Feldman, and Neil Soni, eds. Oxford: Heinemann Medical Books, 1990, 745 pp, $99.95.

The *raison d'être* for this work was set forth in the preface to the first edition: "No attempt has been made to teach the practical, technical aspects of anaesthesia. Our objective has been to complete a volume which covers the scientific foundations upon which are based the clinical practice of anesthesia, resuscitation and the care of acutely ill patients in intensive care units." The fourth edition endeavors to maintain this course while maintaining its size "within reasonable bounds." The latter goal may represent an unfortunate choice, because the book suffers from lack of space in both depth and breadth.

Although the editors present chapters discussing neuroendocrine and metabolic responses to stress, autonomic receptors, and the pathophysiology of shock, there is no chapter describing mediators, such as the prostaglandins. There is a chapter on pain theory and management and one on endogenous opioid peptides, but nothing about intraspinal opiates. There is a 20-page chapter on the electroencephalogram (twice the size of the average chapter), but nothing on evoked potentials.

Some chapters have remained relatively unchanged, as they should. Strickland's two chapters on "physical principles" have been condensed into one chapter in the fourth edition. Physical principles haven't changed much in the past 8 years, and fortunately neither has this excellent chapter. It is almost worth the price of the book to see how wonderfully this topic is presented. Also to Strickland's credit is the new chapter on SI units—perhaps the only such discussion in the world that is not painful to read.

Other encore performances have not fared as well. In the last edition, Leigh presented a lengthy discussion of V/Q relationships and their effect on anesthetic uptake in the chapter entitled "The Pulmonary Circulation"—despite a chapter by West devoted to V/Q relationships and a chapter by Eger (now by Hull) on inhalational anesthetic pharmacokinetics. Leigh's chapter has remained largely unchanged, but our knowledge of pulmonary physiology has not. The editors should have remedied the overlap in this edition, seeking a chapter more like the excellent discussion of the coronary circulation.

Certain new additions do not enhance the fourth edition. Those who wish to learn more about the pathophysiology of shock will not satisfy this goal by reading the chapter entitled "Pathophysiology, Monitoring, Outcome Prediction and Therapy of Shock States." The chapter quickly glosses over any real discussion of shock states and jumps to a skewed dissertation based mainly upon the authors' own work (over half the bibliography consists of papers by the senior author). There is essentially nothing to be found regarding cellular mechanisms in shock (again, one would think that mediators did not exist), and a large portion of the chapter is devoted to treatment and outcome prediction—a seeming violation of the editors' intent with this series.

Despite the international range of the contributors, some chapters are provincial in scope. For example, the chapter on routine monitoring details the Harvard standards, which have not been officially sanctioned, and ignores those standards promulgated by any country's anesthesia society.

On a positive note, I enjoyed reading many of the sections in this book, if only for the pleasure of seeing how most of the authors could meet the challenge of condensing their subject into bite-size morsels with such eloquence. As alluded to above, I question the decision to try to keep the size down. Many comprehensive anesthesia texts have expanded to two or three volumes—an inevitable development given the growth of the specialty—and a book that tries to cover comprehensively the scientific foundations of anesthesia must grow as well. In addition, the increased size of general anesthesiology texts is due in large part to the greater depth of coverage of basic science information, thereby eclipsing a book composed of brief chapters on basic science topics. The previous three editions of this book filled a void with their unique format. With more space and tighter editorial reins, this book could once again be a shining star in the constellation of anesthesia texts. In its present form, it is more suitable as a quick reference to refresh the memory or to review for examinations than as a primary source of information. The typical anesthesiologist might be better served by a copy of a comprehensive anesthesia text, a book about monitoring, and one on equipment—a combination likely to be found on most contemporary practioners' bookshelves already.

Michael S. Gorback, MD
Duke University Medical Center
Durham, North Carolina

Gas Monitoring and Pulse Oximetry

J. S. Gravenstein. Boston: Butterworth-Heinemann, 1990, 148 pp, $21.95.

As suggested by the title of this monograph, gas monitoring and pulse oximetry have become integral to the modern practice of anesthesia: most of us would no sooner begin an anesthetic without a functioning pulse oximeter and capnograph than without a laryngoscope! An understanding of the principles underlying pulse oximetry and intraoperative respiratory gas measurement is essential to the proper interpretation of data provided by these monitors. This text provides concise explanations of these principles with many fine illustrations; however, numerous errors and omissions detract from its overall utility.

After an introduction that stresses the importance of oximetry and respiratory gas monitoring as "early warning" systems, the four phases of normal carbon dioxide waveforms (capnograms) are described, along with those factors that affect the morphology of each phase. There is also a brief discussion of the less-appreciated "oxygram" and "anesthetigram," which provide useful information on the uptake and elimination of oxygen and anesthetics, respectively. Exhaled respiratory gases are saturated with water vapor at body temperature (BTPS), and a chapter is devoted to discussing the effect of water vapor on the analysis of respiratory gases. Although some of the options available for reporting gas concentrations are suggested, the clinician is left without a clue as to what type of data a particular monitoring system provides.

The next several chapters digress from monitoring to discuss the uptake and elimination of respiratory and anesthetic gases. The discussion of time constants is extremely tedious; after incorrectly stating that the time constant "τ can be calculated as $(1 - e^{-1})$," Doctor Gravenstein concludes, "the derivation of which, I cannot supply." The discussion of pulmonary resistance and compliance contains the erroneous assertion that "the greater the resistance, the longer it takes to fill the functional residual capacity with new gas." The effect of blood-gas solubility coefficients on anesthetic uptake is well illustrated with examples generated by the "Gas Man" computer program; however, the discussion is flawed by the following statement regarding nitrous oxide: "We find that the ratio of volume dissolved to the volume in gas phase is as 1 to 0.47."

The use of monitors to detect anesthesia delivery system malfunctions is addressed in the next section. The importance of an oxygen analyzer for detecting disruptions of fresh gas flow is appropriately emphasized. Despite the proportioning devices found in modern anesthesia machines, hypoxia may result from inequalities in the uptake of oxygen and nitrous oxide when fresh gas flows are less than 1 L/min. The effects of defective valves, leaks, and exhausted sodalime on the capnogram are described in detail, with numerous computer-generated illustrations.

The discussion of gas analyzer technology seems to be condensed directly from Doctor Gravenstein's recent text, *Capnography in Clinical Practice* (Boston: Butterworth, 1989); there is, however, an interesting discussion of paramagnetic (Pauling) and polarographic oxygen analyzers. The discussion of pulse oximetry is reasonably comprehensive; unfortunately, errors in the text detract from the overall utility of this section (e.g., "An easy rule of thumb approximates 90% S_pO_2 as P_aO_2 of 60 mmHg and *30%* S_pO_2 as P_aO_2 of 30 mm Hg" [emphasis added—should be *60%* S_pO_2 as P_aO_2 of 30 mmHg]).

In summary, although the concepts discussed in *Gas Monitoring and Pulse Oximetry* are important for all practicing anesthesiologists, the plethora of errors throughout the text are distracting to those who already know the material and confusing for those who are trying to learn.

Jeffrey B. Gross, MD, BSEE
University of Connecticut School of Medicine
Farmington, Connecticut

Perioperative Cardiac Dysrhythmias: Mechanisms, Recognition, Management, 2nd ed.

John Atlee, III. Chicago: Year Book, 1990, 443 pp, $74.95.

Interpreting electrocardiograms might seem like a prosaic task; however, anesthesiologists must perform this task, quickly and accurately, under the most difficult intraoperative conditions. Oftentimes, anesthesiologists buy expensive reference texts written by cardiologists hoping that they will acquire a better understanding of electrocardiographic interpretation.

In 1985, Dr. John Atlee published an award-winning textbook concerning electrocardiograms. The second edition is an improvement both in information and organization. Dr. Atlee begins with a perspective of perioperative cardiac dysrhythmias, then discusses normal and abnormal electrical activity of the heart. The last four chapters develop the clinical aspects of electrocardiography.

Whereas the scientist would examine the second and third chapters dealing with arrhythmogenesis on molecular and cellular levels and marvel at the 2146 references, the clinician will be most interested in the final four chapters. Chapter 4 encompasses not only the methods of obtaining an electrocardiogram signal from the skin, esophagus, endocardium, and epicardium, but also methods of evaluation of dysrhythmias, such as Holter monitoring, stress testing, and electrophysiologic studies. Dr. Atlee logically includes pacemaker electrocardiography in this chapter. Chapter 5 extends an exhaustive list of the intraoperative causes of dysrhythmias to alert anesthesiologists to other medical conditions likely to be associated with dysrhythmias. These other conditions include mitral valve prolapse, long QT syndrome, sick sinus syndrome, and others. Chapter 6 reveals an array of useful therapeutic modalities, including the administration of drugs, pacemakers, cardioversion, and defibrillation. This important chapter examines the relation between the pharmacologic actions of the drugs and the underlying pathologic mechanisms of the dysrhythmia. The book's final chapter could stand alone as a book in itself and is most likely the chapter to be consulted when a quick reference on dysrhythmia recognition and management is needed. The chapter presents an impulse drawn on a diagram of the heart, relates this impulse to the surface and intracavitary electrocardiograms, and discusses how to avoid complications or treat them if they occur.

Perioperative Cardiac Dysrhythmias is a very well-written and affordable book that reveals Dr. Atlee's extensive insight on the subject. It is not just another electrocardiography book, although one could use it as such. It is an important reference text for the scientist and clinician that will impart an in-depth understanding of dysrhythmias, and improve patient care.

James R. Zaidan, MD
Department of Anesthesiology
Emory University
Atlanta, Georgia

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Barash PG, Cullen BE, Stoelting RK. *Handbook of Clinical Anesthesia*. Philadelphia: J.B. Lippincott, 1990, 561 pp, $24.95.

Berry FA, ed. *Anesthetic Management of Difficult and Routine Pediatric Patients*. 2nd ed. New York: Churchill Livingstone, 1990, 457 pp, $45.00.

Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 3rd ed. Baltimore: Williams & Wilkens, 1990, 732 pp, $59.95.

Capan LM, Miller SM, Turndorf H. *Trauma Anesthesia and Intensive Care*. Philadelphia: J.B. Lippincott, 1990, 884 pp, $125.00.

Caussons TR, McKee PA, Williams GR, (eds). *Manual of Medical Care of the Surgical Patient*. Boston: Little Brown Company, 1990, 323 pp, $24.50.

Frost EAM. *Clinical Anesthesia in Neurosurgery*. 2nd ed. Stoneham, Mass.: Butterworth Heinemann, 1990, 593 pp, $98.00.

Gravenstein N, ed. *Manual of Complications During Anesthesia*. Philadelphia: J.B. Lippincott, 1990, 736 pp, $39.50.

Matjasko MJ, Shin B. *Anesthesia and Trauma*. Volume 4, No. 3 of Problems in Anesthesia. Philadelphia: J.B. Lippincott, 1990, 230 pp, $30.00 individual or $65.00 annual subscription for four issues.

North B, Reilly P. *Raised Intracranial Pressure*. Stoneham, Mass.: Butterworths, 1990, 109 pp, $55.00.

Turney SZ, Rodriguez A, Cowley RA, eds. *Management of Cardiothoracic Trauma*. Baltimore: Williams & Wilkins, 1990, 417 pp., $69.00.

Wetchler BV, ed. *Anesthesia for Ambulatory Surgery*. 2nd ed. Philadelphia: J.B. Lippincott, 1990, 720 pp, $69.50.

Classified Advertising

FULL-TIME ANESTHESIOLOGIST
BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to 1415 18th Street, Lake Charles, LA 70601.
497I/B

ILLINOIS
Large, well-established, single-specialty group of anesthesiologists seeks additional BC/BE anesthesiologists. Challenging opportunity for those interested in a broad-based practice. All surgical subspecialties represented. Minimal OB and pain management. Early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 61614.
511J/C

CALIFORNIA
From time to time faculty positions as an Assistant Professor become available in the *Regular Professorial Series (Tenure Track)* in the UCLA Department of Anesthesiology. Candidates are required to show evidence or promise of research productivity and scholarly writing. Other requisites include clinical and teaching skills; commitment to discovery; eligibility for a California Medical License; ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.
526J/C

CALIFORNIA
Faculty positions in the *Clinician-Teacher* Academic Professorial Series in the UCLA Department of Anesthesiology are available. We are interested in all anesthesia subspecialties. Requisites include eligibility for a California Medical License and ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.
527J/C

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY
The Department of Anesthesiology of Columbus Children's Hospital is expanding its fellowship program. Positions are currently available for a 1-year fellowship in pediatric anesthesiology. Children's Hospital of Columbus, Ohio is a 313-bed general pediatric institution with a surgery caseload of 13,000–14,000 cases per year. All pediatric surgical specialities are represented with large case loads in pediatric neurosurgery and cardiovascular surgery. Regional anesthesia in infants and children along with acute/chronic pain management experience is available. An active transplantation service is present. Opportunity for research is provided under the guidance of a full-time director of research. Inquiries should be submitted to J. David Martino, MD, Chairman, Department of Anesthesiology, Columbus Children's Hospital, Columbus, OH 43205.
531K/D

MISSOURI
The Department of Anesthesiology of St. Louis University School of Medicine is seeking board-qualified or certified full-time faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110-0250; telephone (314) 577-8750.
544L/D

CHAIRPERSON—DEPARTMENT OF ANESTHESIA
Kern Medical Center seeks a Chairperson, Department of Anesthesia, who will form a corporation and independently contract for anesthesiologists' services to the Medical Center. The Corporation is to engage six (6) full-time anesthesiologists including the Chairperson. Kern Medical Center is a 240-bed teaching institution with a large emergent, OB and Neuro volume serving as a trauma center. Excellent quality of life is offered in an "All-American" city with a moderate cost of living, warm climate, and varied recreational activities.

Requires board certification, a California license, and five or more years of clinical practice experience. Chairperson will be eligible for a UCLA faculty appointment. Send resumes to Anesthesia Search Committee, Room C-150, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305.
547L/B

ANESTHESIOLOGIST
Board eligible/certified anesthesiologists with California license to join group contracting services for Kern Medical Center, a busy teaching institution in growing area of 350,000 and an "All-American" city. If interested, submit resume to Search Committee, Room C150, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305.
548L/B

MAINE
BC or BE MD to join group of three MD anesthesiologists and four CRNAs, in the

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announcements, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6125.

Rates. Ads cost $1.25 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $17.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia* Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

practice of anesthesia, intensive care and respiratory care. Phone (207) 622-1959 from 8:30 AM to 3:30 PM. Write to Chief of Anesthesia, Kennebec Valley Medical Center, 6 East Chestnut Street, Augusta, ME 04330.

560L/E

BE/BC ANESTHESIOLOGIST

SW PA, 300-bed, modern community hospital to work with 3 MDs and CRNAs. Competitive starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to box 561L/B.

561L/B

NEW YORK

CA 3 or 4 fellowship positions at Memorial Sloan-Kettering Cancer Center beginning July 1991. Straight clinical and clinician–investigator opportunities available in critical care medicine, pain management, and anesthesia for thoracic surgery. Send CV and summary of career goals to Mary E. Fischer MD, Director of Anesthesia Training, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

563L/B

ANESTHESIOLOGIST

BC/BE to join group of 10 MDs with CRNAs in a large hospital located in a pleasant midwestern community on the Great Lakes. Busy practice covering all major surgical subspecialties plus respiratory/ICU involvement and OB. Excellent starting salary and benefits package leading to early partnership. Send CV to Associated Anesthesiologists of Toledo, Inc., 2409 Cherry Street, Suite 4, Toledo, OH 43608.

566A/C

ANESTHESIOLOGY

Come join our medical team! We are a 640-bed medical center located in the heart of Columbus, Ohio. Our hospital offers a full range of anesthesia services including OB, neuro, pain management, and open heart. Over 14,000 anesthesia procedures performed annually. Our service area exceeds 1.5 million people and Columbus is one of the fastest growing areas in the midwest. Our community offers a wide range of cultural opportunities and is currently ranked as the nation's tenth most desirable place to live. We have all the advantages of a major metropolitan area, including access to a noted medical university; or, if you prefer, a chance to unwind with a visit to the quiet and scenic hills of the Ohio Valley. Competitive package and benefits. Address inquiries/forward curriculum vitae to Jim Christian, Grant Medical Center, 111 South Grant Avenue, Columbus, OH 43215; (614) 461-3346.

567AB

LOCUM TENENS

Anesthesiologist, MD. Experienced, AMG, board certified. Will consider permanent situation. Licensed: MO, KS, CO, IA, NC, SC, PA, VA, IL, IN, KY, OH, TN; others pending. PO Box 1176, Kings Mountain, NC 28086; (704) 739-4683 Office, (704) 739-1917 Home.

568A/C

ANESTHESIOLOGISTS

Oklahoma City; 500-bed hospital has positions available for two (2) BC/BE anesthesiologists, each to commit 50% of time to obstetrical services. Obstetric facility is new 19,000-ft unit, two (2) operating rooms with new equipment, postsurgical recovery, 14 LPRP rooms with central and bedside monitoring. Level I and II deliveries, well-trained staff. Hospital provides salary, benefits, and malpractice. Reply Box 569AB.

569AB

CA III POSITIONS IN ANESTHESIOLOGY

The Department of Anesthesia at New England Medical Center Hospitals, Boston, Massachusetts (Tufts University) is accepting applications for CA III positions in adult cardiac anesthesia. This will be a 6-month rotation specializing in all aspects of cardiac anesthesia beginning July 1991 and January 1992. Include CV with letter. Reply to Box 570AB.

570AB

OHIO

Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

571A/F

SOUTHERN CALIFORNIA

Olive View Medical Center, a UCLA-affiliated Los Angeles County hospital, is seeking academically qualified anesthesiologists. Board certified or in process required. Training in OB, pediatrics, or neuro desired. No OH or trauma. Please send CV with three references to Anesthesia Search, Department of Anesthesiology, Olive View Medical Center, 14445 Olive View Drive, Sylmar, CA 91342. Equal Opportunity Employer.

573A/C

ILLINOIS, CHICAGO

Anesthesiologist BC/BE to join expanding group practice limited to outpatient anesthesia. Excellent opportunity for growth. Send CV to Marc Sloan, MD, 25 East Washington, Suite 300, Chicago, IL 60602.

574A/F

ANESTHESIOLOGISTS

Temple University School of Medicine has full-time faculty positions available for board-eligible anesthesiologists with training in a subspecialty area (obstetrical anesthesia, cardiac anesthesia, or neuro-anesthesia and/or critical care). Faculty rank will be commensurate with experience. Duties include patient care, teaching, and research. Send curriculum vitae to Christer Carlsson, MD, Chairman, Department of Anesthesiology, Temple University School of Medicine, Broad and Ontario Streets, Philadelphia, PA 19140. An Equal Opportunity/Affirmative Action Employer.

576AB

CRNA for large regional mid-Michigan hospital. Competitive salary and excellent fringe benefits, including fully paid health and malpractice insurance. Most specialties with high percentage OB/GYN. Ideal Great Lakes location for the sportsperson. Contact Vickie Henige, Saginaw General Hospital, 1447 North Harrison, Saginaw, MI 48602; (517) 771-4502.

578AB

WANTED?

Affable anesthesiologist to join progressive fun-loving department in central Vermont area. Locate in the mountains. See the leaves. 4 MD, 1 CRNA group. We do pain our way. DO IT NOW—send CV to Chairman, Department of Anesthesia, c/o Central Vermont Hospital, PO Box 547, Barre, VT 05641. A limited time offer. Respond now!!

580A/D

ILLINOIS

Seeking three BC/BE well-trained anesthesiologists to join 12 physicians and 15 CRNAs in a busy group practice that includes cardiothoracic, neuro, neonatal, and OB at a 650-bed hospital with an academic affiliation. Subspecialties considered, especially cardiac, pediatric, and obstetrics. Excellent salary and benefits. Send CV to Quentin A. Pletsch, MD, St. John's Hospital, 800 East Carpenter, Springfield, IL 62769.

581AB

ALABAMA—ANESTHESIOLOGIST

Faculty position for clinical BC/BE anesthesiologist at University of Alabama at Birmingham, Department of Anesthesiology. Opportunities to do clinical research, variety of clinical cases including liver transplantation. Desire to participate in teaching necessary. Limited night call. Generous benefit package. Salary competitive with private practice situations. Located in downtown Birmingham; city rated "America's most livable city" by U.S. Conference of Mayors, June 1989, and rated by *Newsweek*, February 1989, as "one of the nation's top 10 hot cities". Please contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205)934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

583AB

CALIFORNIA

The UCLA Department of Anesthesiology has openings for faculty with experience in anesthesia for organ transplantation. Requisites include clinical and teaching skills; eligibility for a California medical license; ABA certification or in process. Address correspondence with names of five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

584A/F

THE UNIVERSITY OF NEW MEXICO

A reorganized, expanding Department of Anesthesiology in the "Land of Enchantment" has seven immediate openings at the Assistant and Associate Professor levels. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to James C. Scott, MD, Associate Professor and Acting Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106, (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

585A/F

General and pediatric anesthesiologists sought for academic medical center practice. Candidates for pediatric position must have experience in all types of pediatric anesthesia. Interest in research and teaching highly desirable. Present staff of 25 MDs, over 40 CRNAs, and over 20 residents provides challenging anesthesia care team setting. OR area contains state-of-the-art equipment in 20 new or renovated suites. Interested applicants should send CV and three references to: Dr. Philip Lumb, Professor and Chairman, Albany Medical College, Department of Anesthesiology, Code A-131, Albany, NY 12208. EOE

592B/F

HONOLULU, HAWAII

Immediate/July opening for a BC/BE anesthesiologist to join a large private practice group. Excellent salary and benefits, including medical/dental, disability and life, professional dues and insurance, generous meeting allowance, relocation expense, profit-sharing, pension plan, and early partnership. Send CV and cover letter to Box 593B.

593B

ANESTHESIA: UNIVERSITY of IOWA, FACULTY POSITIONS at ALL RANKS

Excellent research facilities. Senior advice/consultation readily available. Must be board certified or in the examination process, eligible for Iowa medical licensure. University of Iowa and VAMC dual appointment possible. Submit curriculum vitae to John H. Tinker, MD, Professor and Head, Department of Anesthesia, University of Iowa College of Medicine, Iowa City, IA 52242. The University of Iowa and Veterans Administration Medical Center are Equal Opportunity/Affirmative Action Employers.

594B

ANESTHESIOLOGIST

The Martha's Vineyard Hospital on resort island off Cape Cod is seeking a board-certified anesthesiologist to share hospital practice with one other anesthesiologist. The opening is available immediately. Please send your resume to David F. Federowicz, President, Martha's Vineyard Hospital, Box 1477, Oak Bluffs, MA 02557. Phone (508) 693-0410, Ext. 200.

595B

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF MINNESOTA

The University of Minnesota Departments of Anesthesiology and Physiology are seeking a research scientist for a full-time faculty position. This position is at the rank of Assistant Professor, tenure track. Responsibilities will include the establishment of a research laboratory capable of basic investigation related to anesthesiology, as well as supporting the investigation of basic human muscle disorders. Other responsibilities will include the organization of research activities within the Department of Anesthesiology, teaching of undergraduate and postgraduate students, and assisting in collaborative research efforts.

Candidates must have a PhD degree and a minimum of 2 years experience as an independent investigator in one of the basic sciences related to anesthesia (muscular physiology, neurophysiology, etc.). Clear evidence of collaborative research with clinical investigators will be required. Compensation and benefits will be competitive and dependent on qualifications.

Last date for receipt of applications is February 15, 1991. Send letters of application with the names of three references and curriculum vitae to Chairman, Search Committee, Department of Anesthesiology, University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455.

596B

WISCONSIN

Anesthesiologist BC/BE to work with four MDs in 200+ bed hospital and surgicenter midway between Milwaukee and Chicago. Fee for service. Send CV and references to Dr. I. Romana, PO Box 594, Kenosha, WI 53141.

597B/E

INDIANA

Faculty positions are available at all academic ranks for adult anesthesia. Positions include teaching and administrative responsibilities as well as opportunities to pursue research interests. Experience in pain management and organ transplantation is desirable. All candidates must be board certified or board eligible. Individuals appointed to the tenure track will be required to maintain an active and ongoing research program. Please send curriculum vitae to Robert K. Stoelting, Professor and Chairman, Department of Anesthesia, Indiana University School of Medicine, 1120 South Drive, Fesler Hall 204, Indianapolis, IN 46202-5115. Indiana is an equal opportunity employer.

599B/D

OREGON

Fellowship—Pain Management. July 1991 and July 1992 Fellowship positions available for physicians who have completed clinical anesthesia training. Setting is a multidisciplinary pain management center that deals with the entire range of acute and chronic outpatient and inpatient pain problems. Experience offered in most diagnostic and therapeutic procedures including intraspinal narcotics and stimulators, cryo, regional blockade, PCA. An active research program exists and participation by fellow is encouraged. Please send CV and names of three references to Wendell C. Stevens, MD, Chairman, Department of Anesthesiology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201.

600B/D

NEW HAMPSHIRE

Excellent opportunity for BC/BE anesthesiologist to join two-person group. Surgical cases include OB/GYN, urology, ENT, ophthalmology, Peds, Ortho, and vascular and general surgery. Position open due to enormous growth in surgical base. Partnership position includes competitive compensation and benefit package. NH is a tax-free state that enjoys year-round recreational and cultural opportunities. This position combines a challenging practice with a quality lifestyle that is rare in this age of corporate medicine. For additional information call or write: Martin Rosenberg, Director of Professional Services, Valley Regional Hospital, 243 Elm Street, Claremont, NH 03743; (603) 543-1606.

601B/D

ANESTHESIOLOGIST
Board certified/eligible anesthesiologist needed for a new outpatient Air Force surgicenter located in Montana. No call, weekends, overtime, or holidays. No inpatients, high-risk, OB, or emergencies so you can enjoy all the beauty Montana has to offer. USAF credentialling and contracting requirements apply. If interested, please contact SSgt Morton, (406) 731-4036.

602B

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF CALIFORNIA, SAN DIEGO is recruiting for five faculty positions at all ranks. One position is the Director of the UCSD Pain Management Program. Applicants for this position must have experience in all aspects of inpatient and outpatient pain management and have extensive experience in pain research and treatment. Applicants must demonstrate motivation to expand a pain management center and be able to direct a clinical pain research program involving protocol-driven human studies. The four other positions require experience in teaching and clinical training, patient care, and research interest or experience is preferred. One position requires demonstrated experience in critical care. One position requires subspecialty training and experience in obstetric anesthesia. One of the five positions may be tenured track. Otherwise the positions are non-tenured track. Rank and salary commensurate with experience and based on the UCSD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in anesthesiology and a California medical license is required. Possession of a certificate of special qualifications in critical care medicine or eligibility to take the qualifying exam is required for the critical care position. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770-A, University of California San Diego Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California, San Diego is an equal opportunity/AA employer. All applications received by April 30, 1991 will receive thorough consideration.

603B/D

CONNECTICUT
Northwest Corner. BC/BE anesthesiologist to join physician group in community hospital. Submit CV to Chairman, Department of Anesthesiology, Sharon Hospital, Sharon, CT 06069.

605B

DEPARTMENT HEAD POSITION SEARCH
Experienced anesthesiologist, head of large MD group since 1980 (approx. 20,000 cases last year), looking for department head/director position. Can also establish and staff an entire department with many of my colleagues who are all well trained, experienced, and board certified. Replies to Box 606B/D.

606B/D

BC/BE, recently trained, immediate vacancy. Competitive salary with liberal fringe benefits. Excellent community to raise a family. All types of surgery except open heart. Partnership after one year. Call in evenings (217) 546-2142.

607B

NORTHWESTERN UNIVERSITY MEDICAL CENTER is recruiting faculty at all levels interested in academic careers in anesthesia. Candidates must have completed at least 4 years of postgraduate training and be board certified or in the process of certification. Experience in neuroanesthesia, trauma, obstetrical anesthesia, and evidence of scholarly productivity will be considered in making final selections. A strong residency program with fellowships in all clinical subspecialties makes appointment to this faculty desirable. Northwestern University is an equal employment opportunity/affirmative action educator and employer. Employment eligibility verification required upon hire. Send curriculum vitae and names of three references to Edward A. Brunner, MD, PhD, Professor and Chairman, Department of Anesthesia, Northwestern University Medical School, 303 East Superior Street, Room 360, Chicago, IL 60611.

608B

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:
The unique feature of these tutorials is the small group size. The personalized format with a maximum of four students in a session allows your performance to be evaluated throughout the session and permits you to raise questions for discussion. Tutoring for the written and oral exams are given separately. The sessions are held in San Francisco and New York and are given in blocks of 3 days. FOR THE WRITTENS, essential test-taking skills are taught for dealing with multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, mock orals are practiced using the guided case discussions which meet the Board's stated objectives. All students will receive study programs for use following these sessions. CALL 415-321-1117.

505I/B

J. STEPHENS MAYHUGH AND ASSOCIATES LOCUM TENENS ANESTHESIA SERVICES
Providing top-quality CRNAs to meet your specific needs. Our CRNAs are screened to assure quality in performance as well as personal stability. License verification, curriculum vitae, references procured by us, AANA recertification, malpractice verification are supplied to you. Call 1-800-426-2349 any time.

552L/E

LOCUM-TENENS ANESTHESIOLOGISTS
Earn up to $40,000 more per year than agencies pay. Don't work for an agency. Work for yourself as I do. For details, send name and address to Dr. Monroe, 7035 Highway 6 South, Suite 175-B, Houston, TX 77083.

538KAB

DON'T FAIL THE WRITTEN BOARDS/ITE
New 1990 edition of practice questions (including past board remembered questions), answers, test-taking techniques, and more. We want to help you pass. Order the original, MEDTEXT call 1-800-695-6301 24 hours a day.

590A/F

A WEEKEND OF PRACTICE ORAL EXAMS
Practice exams, not lectures. We are the original course in this format. 20 hours Category I CME credit, two board-certified instructors, 12 students maximum. Tampa, March 1–3; Dallas, March 22–24; Denver, April 5–7. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480.

558B

---

(800) FAST-GAS
The number that hundreds of hospitals nationwide have called for permanent and temporary anesthesia services. The number that thousands of anesthesia professionals have called to secure permanent and temporary positions nationwide. Bay Area Anesthesia, Inc. 1-800-327-8427 for years of professional anesthesia service.

582B/G

Dial 1-800/RENT-A-DOC
For anesthesiologists and CRNAs. We can provide you with quality locum tenens

services to meet your specific coverage needs. Or work locum tenens with us for a change in both your practice and your lifestyle. ReplaceMed * 1-0800/736-8236 * PO Box 640 * Michigan City, IN 46360.

598B/L

FOR SALE
Two 30/70 Proportioner Anesthesia Machines by OHIO with Ethrane, Forane and Halothane TEC 4 vaporizers, CO_2 absorbers and O_2 monitors. Stock #216-7193-800; Serial #BCFM00081/BCFM00090. Six years old with very little use—LIKE NEW. $10,000 each. Quarterly maintenance by Bill Turner, Ohmeda technician. May contact Mr. Turner for reference concerning these machines at 1-800-433-5070. If interested contact Melinda M. Prevost, MD, (504) 767-2417.

604BC

Two full-time faculty positions at the Assistant/Associate/Full Professor level. The position requires abilities appropriate for a University position. Applicants must be board eligible and meet California license requirements. Responsibilities include instruction in the various aspects of anesthesiology; clinical service; clinical and/or basic science research; and publication of scholarly articles. Send curriculum vitae, bibliography and *names of three to five (3–5) references* to Gerald Gronert, MD, Professor and Acting Chair, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. Position open until April 30, 1991. We are an Equal Opportunity/Affirmative Action Employer.

609BC

INDEX TO ADVERTISERS

- Anaquest
  - *Stadol* A13 thru A14
- Anesthesia Partners, Inc.
  - *Recruitment* A35
- Augustine Medical
  - *Bair Hugger* A6
- Burroughs Wellcome Company
  - *Tracrium* A26 thru A28
- The Cleveland Clinic Foundation
  - *Recruitment* A34
- Drug Free America
  - *Corporate* A38
- Georgetown University Medical Center
  - *Course* A28
- Illinois Masonic Center
  - *Course* A37
- Janssen Pharmaceutica
  - *Alfenta* Cover 4
  - *Sufenta* A4
- Medtronic, Inc.
  - *SynchroMed* A33 thru A34
- Northern Health Systems
  - *Computer System* A8
- Organon Pharmaceuticals
  - *Norcuron* Cover 2, A1
- Osler Institute
  - *Course* A15
- Physician Practice Link
  - *Recruitment* A35
- Polamedco, Inc.
  - *Slick Stylette* A2
- Preferred Physicians Mutual
  - *Insurance* Cover 3
- Hoffman La Roche
  - *Versed* A10 thru A12, A31 thru A32
- Shriners Hospital
  - *Recruitment* A34
- Stuart Pharmaceuticals
  - *Diprivan* A17 thru A23
- St. Luke's/Roosevelt Hospital
  - *Recruitment* A35
- University of Missouri Hospital
  - *Recruitment* A36
- University of Texas Health Science Center
  - *Recruitment* A37
- Vanderbilt University
  - *Fellowship* A35

Advertising Office: Pharmaceutical Media, Inc., 440 Park Avenue South,
14th Floor, New York, New York 10016. Telephone: (212) 685-5010

Abstracts of Scientific Papers
1991 Annual Meeting

ISSN 0003-2999
Volume 72, Number 2S, February 1991

Acc 7/93

171

UNIVERSITY MEDICAL LIBRARY

Anesthesia and Analgesia

39A

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N. C. 27709

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

March 1991

Burroughs Wellcome Co. has demonstrated a long-term commitment to the research and development of neuromuscular blocking agents as adjuncts to anesthesia starting in 1952 and continuing with the introduction of TRACRIUM® (atracurium besylate) in 1983.

Of all the agents in its class, Tracrium has the shortest elimination half-life (approx. 20 min.). Rapid elimination of Tracrium means easy reversal and fast, complete recovery.

In short and long procedures and in a wide range of patient types, its unique metabolism—unaffected by renal or hepatic dysfunction—gives Tracrium the most consistent pharmacodynamic profile of any nondepolarizing neuromuscular blocker.

We continue to remain active in the research and development of new neuromuscular blocking agents and recognize the need for the scientific presentation of results from on-going medical research. Therefore, Burroughs Wellcome Co. is pleased, once again, to support the publication of quality research as exemplified by the abstracts submitted for presentation during the International Anesthesia Research Society Sixty-Fifth Congress, March 1991.

Yours sincerely,

Richard Kent

Richard Kent, MD
Medical Director

P.S. Please see brief prescribing information following our advertisement.

Neuromuscular blocking agents for the ICU: How do they compare?

	TRACRIUM	vecuronium	pancuronium
Good cardiovascular profile in surgical patients?	**YES**	**YES**	**NO** (vagolytic)[1]
Elimination half-life (based on single-dose kinetics)	**20 minutes**[2] (approximate)	**65 to 75 minutes**[3]	**89 to 161 minutes**[1]
Nonhepatic/non-renal mode of elimination...	**YES**	**NO**	**NO**
...unaltered by renal or hepatic dysfunction?	**YES**[2,6]*	**NO** significantly prolonged[3-6]*	**NO**[7]* doubled[1]
Rapid recovery after infusion even in patients with renal failure?	**YES** 47 to 105 minutes in five renal failure patients after 15-37-hr. infusion[6]	**NO** 6 to 37 hours in six renal failure patients after 7-32-hr. infusion[6]	**Infusion not recommended**[7]
Ready-to-use convenience?	**YES**	**NO** requires reconstitution	**YES**

TRACRIUM® *INJECTION*
(atracurium besylate)

Uniquely suited for infusion in the ICU

* As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of metabolites following long-term (days to weeks) administration.

Please see brief summary of prescribing information on the next page.

TRACRIUM® INJECTION
(atracurium besylate)

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: **General:** Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: **Observed in Controlled Clinical Studies:** Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

1. Package insert, Pavulon® (pancuronium bromide).
2. Package insert, Tracrium® Injection (atracurium besylate).
3. Package insert, Norcuron® (vecuronium bromide).
4. Lynam DP, Cronnelly R, Castagnoli KP, Canfell C, Caldwell J, Arden J, et al. The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. *Anesthesiology.* 1988;69:227-231.
5. Lebrault C, Duvaldestin P, Henzel D, Chauvin M, Guesnon P. Pharmacokinetics and pharmacology of vecuronium in patients with cholestasis. *Br J Anaesth.* 1986;58:983-987.
6. Hunter JM. Infusions of atracurium and vecuronium in patients with multisystem organ failure in the intensive therapy unit. *Insights into Anaesthesiology.* 1987;1:23-27.
7. Hunter JM. Neuromuscular blocking drugs in intensive therapy. *Intensive Therapy and Clinical Monitoring.* 1989;10:147-152.

Burroughs Wellcome Co.
Research Triangle Park, NC 27709
Wellcome Copr. © 1990 Burroughs Wellcome Co. All rights reserved. TR021

IARS REVIEW COURSE LECTURES AVAILABLE

____ 1990, 64th Congress—26 Review Course Lectures—$10.00

____ 1989, 63rd Congress—27 Review Course Lectures—$10.00

____ 1988, 62nd Congress—26 Review Course Lectures—$10.00

____ 1987, 61st Congress—25 Review Course Lectures—$6.00

____ 1986, 60th Congress—26 Review Course Lectures—$6.00

____ 1985, 59th Congress—26 Review Course Lectures—$6.00

____ 1984, 58th Congress—24 Review Course Lectures—$6.00

____ 1983, 57th Congress—16 Review Course Lectures—$5.00

____ 1982, 56th Congress—14 Review Course Lectures—$5.00

To:
International Anesthesia Research Society
Suite 140, 2 Summit Park Drive
Cleveland, Ohio 44131-2553

Please send Lecture Booklets checked above.

My check, payable to IARS in the amount of $________ is enclosed.

____
(Name)

____
(Mail Address)

____

____
(City, State, Zip)

Acc. 7 7/73

UNIVERSITY COLLEGE LIBRARY

Anesthesia and Analgesia

Journal of International Anesthesia Research Society

Suite 140, 2 Summit Park Drive, Cleveland, Ohio 44131-2553 Telephone: (216) 642-1124

Editorial Board

Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada

Phillip O. Bridenbaugh, MD, Cincinnati, Ohio

Mieczyslaw Finster, MD, New York, New York

Thomas J. Gal, MD, Charlottesville, Virginia

Paul R. Hickey, MD, Boston, Massachusetts

Edward D. Miller, Jr, MD, New York, New York

Walter S. Nimmo, MD, BSc, FRCP, FFARCS, Edinburgh, Scotland

Nathan L. Pace, MD, Salt Lake City, Utah

Richard J. Palahniuk, MD, Minneapolis, Minnesota

Ronald G. Pearl, MD, PhD, Stanford, California

Donald S. Prough, MD, Winston-Salem, North Carolina

Joseph G. Reves, MD, Durham, North Carolina

John J. Savarese, MD, New York, New York

John H. Tinker, MD, Iowa City, Iowa

Barbara E. Waud, MD, Worcester, Massachusetts

Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Manuscripts should be addressed to: RONALD D. MILLER, MD, *Anesthesia and Analgesia*, University of California, San Francisco, 521 Parnassus Avenue, Room C-450, San Francisco, CA 94143-0648. For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 655 Avenue of the Americas, New York, NY 10010; prices on request.

All articles published in this Journal become the property of the International Anesthesia Research Society. This journal has been registered with the Copyright Clearance Center, Inc. Consent is given for the copying of articles for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay through the Center the per-copy fee stated in the code on the first page of each article for copying beyond that permitted by the US Copyright Law. If no code appears on an article, the author has not given broad consent to copy, and permission to copy must be obtained directly from the author. This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works.

On-line text is available through BRS Colleague, 8000 Westpark Drive, McLean, VA 22102; telephone (800) 289-4277.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, Edward D. Miller, Jr, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K. C. Wong, MD, PhD. Emeritus Trustees are: Paul R. Dumke, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Morris J. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1991 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year, in all other countries $110.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited by anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, and students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: International Anesthesia Research Society, Suite 140, 2 Summit Park Drive, Cleveland, Ohio 44131-2553.

Subscription information for 1991 applying to non-IARS members: Institutions, $140.00; nonmember individuals, $100.00. Outside of the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico, $55.00 for surface airlift to Europe, $75.00 for surface airlift to Japan, and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical sciences, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

This journal is printed on acid-free paper.

IARS MEMBERSHIP

FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a nonprofit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end, the IARS

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March

Funds projects in anesthesia-related research, clinical care, education, and administration through the B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, or national anesthesia organization. Membership is open to individuals who qualify in the various categories shown below. All memberships include a monthly subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee. Only IARS members may apply for the B.B. Sankey Anesthesia Advancement Award.

MEMBERSHIP CATEGORIES

MEMBERSHIP: Open to individuals with doctorate degrees who are licensed to practice in the medical, osteopathic, dental, or veterinary medicine fields (i.e., MD, MB, DO, DDS, DVM); and to individuals with doctorate degrees (PhD) in any scientific discipline who are engaged in academic, private, or commercial research.

ASSOCIATE MEMBERSHIP: Open to individuals in the allied health professions who are certified by their professional accrediting organization as nurse anesthetists (CRNA), respiratory therapists or technicians (RRT or CRTT), physician assistants (PA, MMS), and other allied health professionals in anesthesia-related practice.

Annual (1991 Calendar Year) Dues for Members and Associate Members: $90 ($110 foreign).

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists, or technicians.

Annual Dues for Educational Members: One-half of the member rate. These memberships are entered in January or July for 2-, 3-, or 4-year periods. Official application, certified by program directors, must be used and submitted with check to cover full membership period.

International Anesthesia Research Society
Suite 140-2 Summit Park Drive, Cleveland, Ohio 44131-2553

Please send me______application(s) for:

☐ Membership ☐ Associate Membership ☐ Educational Membership

Please print clearly:____
Name and Degree / Certification

____
Street Address City, State, Zip Code (country)

Anesthesia
and Analgesia

Abstracts of Papers and Posters Presented at the International Anesthesia Research Society 65th Congress

San Antonio, Texas
March 8–12, 1991

Abstracts:	S1–S336
Author Index:	S337–S349
Subject Index:	S350–S355

Authors submitting abstracts have certified that if human research is reported, approval by an institutional human research committee has been obtained, or if animal research is reported, the usual standards and guidelines for animal care have been followed. Material published in this supplement has not undergone review by the Editorial Board of Anesthesia and Analgesia.

Journal of the International Anesthesia Research Society

S1

TITLE: PHENYLEPHRINE DOES NOT LIMIT MYOCARDIAL O_2 DELIVERY DURING ISOFLURANE-INDUCED HYPOTENSION IN DOGS

AUTHORS: M Abdel-Latif, MD, S-J Kim, MS, MR Salem, MD, GJ Crystal, PhD
AFFILIATION: Depts of Anes, IL Masonic Med Ctr & Univ IL Coll Med, Chicago, IL 60657

Although α_1-adrenoreceptors are present in the coronary circulation (1), it is uncertain whether they mediate a local vasoconstrictor response when phenylephrine (PHEN) is infused to treat anesthetic-induced hypotension. Such vasoconstriction may have adverse effects on myocardial oxygenation. The present study was performed to evaluate influence of PHEN on indices of myocardial O_2 supply/demand balance during isoflurane-induced hypotension.

After approval of our Institutional Animal Investigation Committee, five mongrel dogs were anesthetized with fentanyl and pentobarbital, left thoracotomized, and mechanically ventilated. Measurements were obtained of mean aortic pressure (MAP), heart rate (HR), left ventricular dP/dt max, and aortic blood flow (AOF). Radioactive microspheres were used to measure mean left ventricular myocardial blood flow (MBF) and its transmural distribution (ENDO/EPI). Blood from aorta and coronary sinus was analyzed for PO_2, O_2 content, and lactate (LAC). Myocardial oxygen consumption (MVO_2) was computed with Fick equation. Measurements were obtained 1) under control, 2) after 30 min inhalation of isoflurane (ISO) sufficient to reduce MAP by 30 %, and 3) while maintaining ISO, 5-10 min after restoration of MAP by intravenous infusion of PHEN.

ISO-induced hypotension was accompanied by decreased AOF (-26%), and dP/dt max (-36%), and increased HR (+31%). MVO_2 and MBF decreased, although decrease in MBF did not quite reach statistical significance. LAC ext. was unaffected (Table 1). PHEN returned MAP and HR to control levels, but AOF and dP/dt max remained reduced. Neither MVO_2, MBF, nor LAC ext. were changed from values during ISO alone.

In conclusion, the relatively parallel changes in MVO_2 and MBF during ISO-induced hypotension are consistent with intact metabolic control of myocardial perfusion (1). PHEN infusion to restore MAP during ISO caused no change in MVO_2, and also did not alter the relationship between MVO_2 and MBF. These latter findings suggest no direct vasoconstrictor effect for PHEN in the coronary circulation exposed to ISO.

Reference

1. Marcus ML. The Coronary Circulation in Health and Disease. MacGraw-Hill, 1983

Table 1. Effects of isoflurane and adenosine.

	CONTROL	ISO ALONE	PHENYL-ISO
MAP, mmHg	107±7	75±2*	107±3
MBF, ml/min/100g	68±8	58±9	59±13
ENDO/EPI	1.1±0.1	1.0±0.1	1.0±0.1
MVO_2, ml/min/100g	8.7±0.6	6.7±1.0*	6.0±0.6*
A-V O_2, vol. %	13.2±0.7	11.6±0.4	11.1±1.1
CS PO_2, mmHg	29±1	32±2	33±2
LAC ext., %	43±11	43±10	45±10

Values are Mean±SE. * $P<0.05$, from Control (ANOVA and Student-Newman-Keuls test).

S2

TITLE: A NOVEL α_2-AGONIST, DEXMEDETOMIDINE AS INTRAMUSCULAR PREMEDICATION FOR LAPAROSCOPY

AUTHORS: Aho M.,M.D.,Lehtinen A-M.,M.D., Erkola O.,M.D., Korttila K., M.D.
AFFILIATION: Women's Hospital, University of Helsinki, SF-00290 Finland

Introduction: A novel highly selective α_2-agonist, dexmedetomidine (dex) has sedative effects[1] and is well tolerated in human volunteers.[2] A single intravenous bolus given 10 min before the induction of anesthesia, attenuated the hemodynamic response to laryngoscopy and intubation and decreased the isoflurane requirements during abdominal hysterectomy.[3] I.v. dex has also diminished the need of thiopental during cervical dilatation and currettage of uterus.[4] This study evaluated the usefulness of dex as intramuscular premedication in patients undergoing diagnostic laparoscopy.

Methods: This double-blind study was approved by the Ethical Committee of the Hospital and comprised 100 consenting healthy women, randomly allocated to five groups, of 20 patients. Every patient received an intramuscular premedication 45-60 min before the induction of anesthesia. The women in study groups received dex 0.6, 1.2 or 2.4µg.kg^{-1}. For comparison separate groups of patients were treated with oxycodone 0.13mg.kg^{-1} or saline. During the premedication period, sedation scores (1=awake,eyes open; 2=asleep easy to arouse; 3=asleep difficult to arouse; 4= not arousable) were estimated 20 and 40 min after administration of the study dose. Preoperative anxiety- and sedation scores were assessed before and after preanesthetic medication, using the POMS (profile of mood states) questionnaire.

Prior to induction of anesthesia glycopyrrolate 0.2mg and vecuronium 0.6mg were administered. Induction was performed with a fixed dose of thiopental, 4.5mg.kg^{-1}, and succinylcholine was given to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane at a standard 0.3% end tidal concentration in 30/70% oxygen-N_2O-mixture. Vecuronium was used to maintain 80% relaxation. The laparoscopy began no sooner than 15 min after intubation and was performed at a standard 15% headdown tilt. Blood pressure and heart rate were measured noninvasively. In the recovery room fentanyl 0.05 mg incremental doses were given for moderate to hard pain and droperidol against emesis if needed. Atropine was given, if the heart rate fell below 45/min. Analysis of variance (ANOVA), followed by Scheffes contrast test, was used to compare hemodynamic changes and Kruskall-Wallis test was used for nonparametric data.

Results: Patient characteristics and the main results are shown in Table. The results of dex 0.6µg.kg^{-1} did not differ from those of the saline group in any respect. Dex 2.4 µg.kg^{-1} relieved anxiety before surgery and caused sedation, as assessed by POMS or by a nurse. During premedication period dex 1.2 and 2.4 µg.kg^{-1} reduced blood pressure compared to saline and both these doses as well as oxycodone reduced heart rate. After laryngoscopy and endotracheal intubation the maximal increase in blood pressure was attenuated in the women premedicated with 2.4 µg.kg^{-1} and the increase in heart rate was attenuated in the women premedicated either with dex 1.2 and 2.4 µg.kg^{-1} or with oxycodone compared to the saline group. Only the dex doses were able to blunt the heart rate response when compared to the values obtained just before the induction of anesthesia. During the laparoscopy only dex 2.4 µg.kg^{-1} was able to significantly reduce the maximal increase in blood pressure values. Both dex doses and oxycodone reduced the increase in heart rate values. In the recovery room oxycodone group needed less fentanyl compared to the other groups. Dex 2.4 µg.kg^{-1} group had less emesis and required droperidol significantly less than the other groups.

Discussion: Based on these preliminary results intramuscular dex premedication appears to have anxiolytic and sedative properties. It also attenuates potentially harmful cardiovascular reflexes caused by laryngoscopy and endotracheal intubation or by laparoscopy. Dex 2.4µg.kg^{-1} decreases heart rate and 8 patients of 20 needed atropine for bradycardia (heart rate <45). No other ECG changes than sinus bradycardia was noticed during this study.

TABLE: MAIN RESULTS Means±SE

	Saline	Oxycodone 0.13mg/kg	Dexmedet 1.2µg/kg	Dexmedet 2.4µg/kg
No of patients	20	20	20	20
Δ Sedation scores**	0.15±0.1	0.45±0.1□	0.25±0.1	0.85±0.1□□
Δ POMS scores: sedation**	0.11±0.1	0.37±0.1	0.11±0.1	0.78±0.1□□
anxiety	0.24±0.1	0.65±0.1	0.56±0.1	0.59±0.1
Max Mean BP after intub**	130±3	122±4	122±4	105±4□
Max HR after intubation**	116±4	106±4□	100±3□	85±2□
Max Mean BP during scopy*	113±4	112±4	106±3	99±4□
Max HR during scopy**	106±4	95±3□	95±3□	80±2□
# of pts having emesis	9	13	8	5
#of pts requiring droperidol*	5	8	3	0
#of pts requiring atropine*	0	0	0	8

*$p<0.05$ and **$p<0.01$ between groups □$p<0.05$ and □□$p<0.01$ vs saline

References:

1. Br J Clin Pharmacol 24:443-451,1987
2. Curr Ther Res 415:637-646,1987
3. Anesth Analg Suppl 70: 25:S5,1990
4. Anesth Analg 70:407-413, 1990

S3

TITLE: TEMPORAL CORRELATION BETWEEN TOXIC PLASMA & URINARY INORGANIC FLUORIDE LEVELS AND URINARY PGE2 IN THE EWE

AUTHORS: D. Albala, M.D.*, D. Coombs, M.D.†, R. Colburn, B.S†, P. Del Guidice, M.D.†.
AFFILIATION: Departments of Surgery (Urology)* and Anesthesiology†
Dartmouth Hitchcock Medical Center, Hanover, NH

Metabolism of volatile anesthetic agents such as methoxyflurane and enflurane can be associated with release of nephrotoxic concentrations of inorganic fluoride (Fl.) and an associated high output renal failure. We were interested whether this diuretic state originated via a prostaglandin-induced inhibition of ADH action in the renal collecting duct. Methods: The investigation was approved by the Institution's Animal Use Committee. This phenomena was studied in five Scottish Black Face ewes by intravenous infusion of sodium fluoride, 150 mg/hr, to acheive serum Fl. levels 175- 200 uM/L (roughly twice the serum Fl. level associated with the initation of high output failure). The urinary bladder was catheterized, a chronic venous access system established, and serial serum Fl. levels, urinary volume, Fl, and PGE_2 were measured. Inorganic Fl levels were measured in duplicate with digital pH meter and a Fl^- specific electrode (Orion Model 701 Ionalyzer and Orion Combination Electrode, Model 96-09-00 Cambridge, MA) and calculated from standard reference curves. PGE_2 samples were collected on ice, in PVC tubes with Indomethacin Na added to establish a 10^{-7} M solution (urin had 10^{-6} Indomethacin Na added to PVC collection bag) and analyzed by RIA (NE Nuclear). Descriptive analysis (means and S.D) and paired T-Test were employed with p<.05=Significant. Results:Baseline serum Fl was undetectable in all ewes. Following Na Fl infusion, the peak serum Fl levels rose to 280 ± 45.0 uM/L.Urinary Fl levels increased dramatically from an undetectable baseline to a peak of 8500 ± 5.2uM/L at 180 minutes following initiation of Na Fl infusion. Serum Fl levels exceeded 40 uM/ML for at least 7 hr in all ewes. A diuretic state ensued in all ewes with an increase of urin output from a baseline of 14.5 ± 2.7 ml/hr before infusion to 45.4 ± 20.8 ml/hr after. Urinary PGE_2 levels promptly increased significantly to a mean peak of 432 ± 295 pg/ml from baseline of 85 ± 29 pg/ml (p< .03). Urinary PGE_2 levels rose synchronously with the urinary Fl levels but in contrast were sustained above highest baseline levels only 4 2/3 hr on average.

Discussion:A toxic increase in serum Fl levels yields a prompt rise in urinary Fl and PGE_2 and corresponding diuresis. The diuresis is sustained well beyond the short period of PGE_2 release. This suggests that though PGE_2 might initiate diuresis by inhibiting the action of ADH on the collecting duct,this effect is likely transient and unlikely to sustain the high output syndrome. Alternatively, Fl may have a special predilection for the fluid balance functions of the nephron, ie collecting duct etc, or increase Atrial Naturietic Factor release to sustain diuresis.

S4

Title: EFFECT OF SUCCINYLCHOLINE ON PLASMA POTASSIUM, ELDERLY VS. YOUNG.

Authors: H.H. Ali, M.D., N.G. Goudsouzian, M.D.
Affiliation: Department of Anesthesia, Harvard Medical School at the Massachusetts General Hospital, Boston, MA 02114.

The dose response and plasma concentration-response relationship for non-depolarizing muscle relaxants does not significantly differ comparing elderly patients (E, >75 y) with their younger cohorts (Y, 25-60 y). This is despite the reduction in skeletal muscle mass in the elderly. Therefore, it can be theorized that there is an apparent resistance to non-depolarizing relaxants in E that may be related to the associated disseminated neurogenic atrophy and the increased numbers of cholinergic receptors. This may suggest increased sensitivity to depolarizing relaxants with potential rise in potassium (K^+). This study is aimed at checking this hypothesis by measuring serial plasma K^+ levels before and after succinylcholine (Sch).

Two groups of 25 ASA I-II surgical patients were studied after obtaining a written informed consent of an institutionally approved protocol. Group I, 15 (E) patients 73±1.7 (SEM) years weighing 69±30 kg and Group II, 10 (Y) patients 37±3.9 years and weighing 72±4.0 kg. They were free from susceptibility to Sch induced hyperkalemia and on no medication to influence plasma K^+. A control plasma K^+ was obtained prior to setting the I.V. infusion. Both groups were medicated with midazolam 1-2 mg and fentanyl 2 ug/kg. Anesthesia was induced with pentothal 3-5 mg/kg and 66% N_2O in oxygen. Tracheal intubation was facilitated with Sch 1.0 mg/kg and anesthesia was maintained with 70% N_2O in oxygen and controlled ventilation to maintain normal end tidal CO_2. EKG, blood pressure, oxygen saturation and body temperature were monitored continuously. Four venous blood samples were collected from a separate cannula in the other arm at 1, 3, 5, and 10 minutes after Sch injection. Plasma K^+ was compared at these time intervals with the baseline and with each group using two-tailed, two-sample student's t-test. Significance was considered at $P < 0.05$.

At 3, 5, and 10 minutes, there was an average increase of 0.3 mmol/L in plasma K^+ in (E). This is lower than the 0.55 mmol/L reported earlier[1] in normal patients. In the younger age group this consistent change could not be demonstrated (Table). This study suggests that the denervation phenomenon in the elderly may not be enough to cause a clinically significant rise in plasma K^+. The consistent rise in plasma K^+ might have theoretical implications but does not contraindicate the use of Sch in the elderly population.

Changes in Plasma K^+ (mmol/L)±SEM

		minutes		
	Baseline	3	5	10
E	3.78±0.09	0.26±0.06**	0.32±0.09*	0.28±0.03**
Y	3.62±0.07	0.16±0.08	0.09±0.09	0.14±0.03

** $P < 0.005$; * $P < 0.001$.

References: 1. Br J Anaesth 41:1048, 1969.

S5

Title: **Rates of Awakening from Desflurane or Propofol in Human Volunteers**

Authors: JL Apfelbaum, MD, JL Lichtor, MD, B Lane, BS, DW Coalson, MD, A Uitvlugt, MD, G Rupani, MD, B Schreider, MD, PhD, B Glosten, MD, MF Roizen, MD, R Finn, MD

Affiliation: Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL (Supported in part by Anaquest)

Introduction: Desflurane (D) is a new potent inhalational anesthetic with an extremely low blood/gas partition coefficient (0.42). Animal studies have demonstrated that the rate of recovery from D is 3 to 10 times as rapid as recovery from the other commonly used volatile anesthetics,[1] suggesting that this agent might be particularly advantageous for use in the ambulatory surgery population. We undertook this study to compare the recovery profile of D with that of propofol (p) in healthy human volunteers.

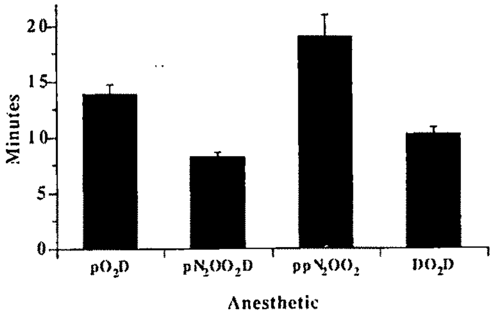
Methods: Twenty healthy male volunteers participated in this randomized, prospective, cross-over trial. The study was approved by our IRB and written consent was obtained from each subject. The subjects were studied with a minimum one week wash-out period between anesthetics. On each test day, each subject received one of four different one hour general endotracheal anesthetics: induction with propofol followed by D/O_2, $O_2/N_2O/D$, or p infusion O_2/N_2O for maintenance; or induction with D/O_2 followed by D/O_2 maintenance. Anesthesia maintenance was titrated to clinical effect so that blood pressure was within 20% of baseline and the volunteers did not move. Sixty minutes after induction, all anesthetic agents except O_2 were discontinued and the following parameters of immediate recovery were measured: responses to command--squeeze hand (SH), open eyes (OE); orientation to name (N), date of birth (DOB), and place (P). Repeated measures analysis of variance was used to assess drug and time effects after anesthesia.

Results: All tested measures of immediate recovery (SH, OE, N, DOB, P) were more rapid in all groups for which D was used for maintenance ($p < 0.001$).

Discussion: Rapid recovery from a p-based anesthetic has made this IV agent a strong addition to the drugs used for anesthesia in the ambulatory surgical population. This current study suggests that recovery from a D-based anesthetic may be even more rapid. Further studies comparing these agents in the ambulatory surgical population appear to be indicated.

Reference: Anesth Analg 66:977-982, 1987

Figure. Time to orientation after discontinuation of anesthetic. Time to orientation was greater for pO_2D than DO_2D ($p < 0.025$); for pO_2D and DO_2D than pN_2OO_2D ($p < 0.01$); and for ppN_2OO_2 than pO_2D, DO_2D and pN_2OO_2D ($p < 0.001$).



S6

TITLE: RECOVERY AFTER PROPOFOL, MIDAZOLAM, AND METHOHEXITAL AS AN ADJUNCT TO EPIDURAL ANESTHESIA

AUTHORS: P.G. Atanassoff, M.D., E. Alon, M.D., P. Biro, M.D., J. Schawalder, M.D., T. Pasch, M.D.

AFFILIATION: Department of Anesthesiology, University Hospital, Zurich, Switzerland

The goal of this clinical investigation was to compare the sedative effects of propofol, midazolam, and methohexital with particular emphasis on postoperative vigilance and power of concentration in patients undergoing lower abdominal surgery under epidural anesthesia (EDA).

Methods. After institutional approval and informed consent, 45 female patients (ASA class 1 and 2) were randomly allocated to four groups. After premedication with promethazine (25 mg i.m.) a lumbar epidural block was performed with bupivacaine 0.75%. Group A (n = 15) was sedated with propofol, group B (n = 11) with midazolam, and group C (n = 11) with methohexital. Group D (n = 8) did not receive any sedative medication. Vigilance and power of concentration were assessed by a modified Bourdon-Wiersma test (1) the day before surgery, on admission to the recovery room, two hours later, and the next morning. Response time was defined as the time from the end of infusion to opening the eyes upon command and giving the date of birth. The Mann-Whitney test was employed for statistical analysis.

Results. There were no differences in the anthropometric data between the groups. Quality and ease of control of sedation were good for all groups. Ventilatory side effects were not observed. In group B, $PaCO_2$ was statistically significant higher than in group D. Three patients in group B and one patient in group C showed restlessnes during and after surgery. The results are shown in the table.

Discussion. This study shows that a continuous infusion of any of the three drugs employed provides good and easily controllable sedation during EDA. Recovery from sedation was faster after propofol than after midazolam and methohexital. While the vigilance was decreased to the same extent by each of the drugs, methohexital caused a more prolonged reduction in concentration than propofol and midazolam.

Reference
1. Korttila K (1976) Modern Problems in Pharmacopsychiatry 2: 91

TABLE INFUSION AND RECOVERY DATA (MEAN ± SEM)

		Propofol (n=15)	Midazolam (n=11)	Methohexital (n=11)	Control (n=8)
Duration of procedure (min)		160 ± 4	154 ± 2	165 ± 3	158 ± 2
Duration of infusion (min)		143 ± 19	131 ± 14	143 ± 17	-
Infusion rate (mg/kg/h)		2.86 ± 0.4	0.09 ± 0.01	1.60 ± 0.2	-
Response time (min)		6 ± 2. 0&	19 ± 4.0	12 ± 4.0	-
Vigilance (dots of four) absolute	preop	34 ± 3	35 ± 3	33 ± 3	35 ± 2
	postop.	18 ± 4 *	18 ± 4 *	18 ± 3 *	36 ± 6
	after 2 h	26 ± 3 +	28 ± 3 +	25 ± 3 +	36 ± 4
	after 24 h	31 ± 3	30 ± 3	27 ± 3 ++	37 ± 6
Concentration (dots of four) relative	preop.	0.96±0.01	0.95±0.01	0.95±0.02	0.93±0.02
	postop	0.92±0.03=	0.85±0.01	0.79±0.07¢	0.96+0.02
	after 2 h	0.95±0.01=	0.92±0.02=	0.80±0.05#	0.96±0.01
	after 24 h	0.92±0.02	0.89±0.05	0.89±0.03¢	0.97±0.02

+ $P < 0.05$ vs control ¢P < 0.02 vs control = $P < 0.05$ vs methohexital
++P < 0.02 vs control * $P < 0.01$ vs control # $P < 0.01$ vs control
& $P < 0.01$ vs midazolam

S7

Title: Differences in pH management and pulsatile/non-pulsatile perfusion during cardiopulmonary bypass do not influence renal function

Authors: NH Badner MD, JM Murkin MD, P. Lok RRT.

Affiliation: Department of Anaesthesia, University Hospital University of Western Ontario, London, Ontario, Canada

Introduction: Recent debate regarding optimum pH management and the use of pulsatile or nonpulsatile perfusion during cardiopulmonary bypass (CPB) has centered on cerebral perfusion and outcome. We are aware of studies looking at these factors indepently,[1,2] but to our knowledge no study has simultaneously compared these two factors with respect to renal function.

Methods: After institutional approval and following written informed consent, patients undergoing elective coronary artery bypass surgery were randomly assigned to receive either pH-stat or alpha-stat pH management and either pulsatile or nonpulsatile perfusion during CPB. Patients with preexisting renal dysfunction (BUN > 12.1 mmol/L or creatinine > 168 μmol/L) or those having received diuretics on the operative day were excluded.

Patients recieved a narcotic general anesthetic. Acid-base balance was measured both on-line and by radial arterial sampling. Pulsatile perfusion was created using a Cobe pulsatile perfusion module which created a pulse pressure of 10-20 mm Hg with a frequency of 60-80 pulse/minute. Urine output (U/O) was measured by an indwelling Foley catheter. Determinations of fractional excretion of sodium (FeNa) or potassium (FeK) as well as renal failure index (RFI)[3] were made prebypass, during CPB, and following discontinuation of CPB.

Results: Presently, 44 patients have been studied. There were no statistically significant differences amongst the four groups with respect to patient demographics, pathology, hemodynamics before or during CPB, preoperative renal function as well as surgical approach and/or time. There were no statistically significant differences in U/O, FeNa, FeK or RFI before, during or after CPB amongst the four groups (see table for CPB results).

Renal Function During CPB

	pulsatile		non-pulsatile	
	alpha-stat	pH-stat	alpha-stat	pH-stat
n	14	10	10	10
U/O	278±48	178±34	380±98	408±138
FeNa	1.46±0.98	0.87±0.25	3.0±1.3	1.54±0.90
FeK	0.60±0.11	0.39±0.03	0.73±0.19	0.47±0.13
RFI	0.74±0.60	0.26±0.43	0.76±0.32	0.38±0.21

values are mean ± SEM, NS differences.

Discussion: No discernable difference in renal function during CPB was detected when using pulsatile/non-pulsatile perfusion or pH-stat/alpha-stat pH management.

References:
1. **J Cardiothoracic Anesth 3:S1:57, 1989**
2. **J Thorac Cardiovasc Surg 68:138-47, 1974**
3. **Acute Renal Failure, in Diseases of the Kidney, Eds RN Schrier, CW Gottschalk, Chp 48, 1413-46, Little, Brown& Co, Boston, 1988**

S8

TITLE: EFFECTS OF HALOTHANE, ENFLURANE AND ISOFLURANE ON THE FERRET CARDIAC LENGTH-TENSION RELATION

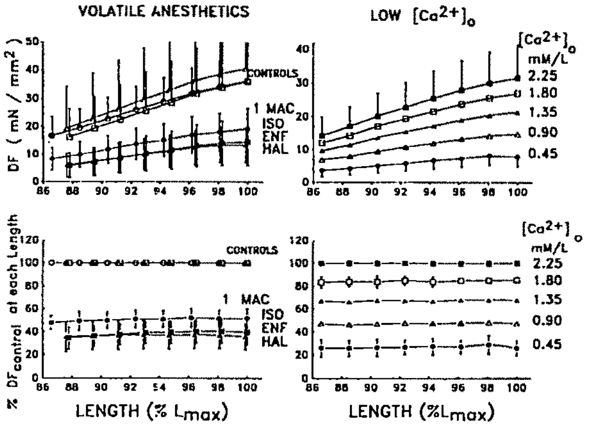
AUTHORS: PL Baele, M.D. and PR Housmans, M.D., Ph.D.
AFFILIATION: Dept. Anesthesiology and Pharmacology, Mayo Foundation, Rochester, MN 55905

The volatile anesthetics (VA) halothane (H), enflurane (E) and isoflurane (I) decrease myocardial contractility in a concentration-dependent fashion (1-2). A decrease in fiber length also reduces force developed (DF) by cardiac muscle fibers. After institutional approval, the interaction of these two interventions was studied by examining the effects of H, E, and I on the length-tension relation of 27 electrically stimulated (0.25 Hz, 30°C) right ventricular ferret papillary muscles. The force-length relationship was derived from isometric twitches at 8 lengths equally spaced from 100% to 86% of L_{max} in each muscle at five calcium concentrations, from 0.45 to 2.25 mM, and at seven concentrations of one VA, from 0 to 1.5 MAC. For each condition the relation between muscle length and 1) absolute values of DF and 2) $DF/DF_{control}$ at each length was analyzed by least squares linear regression analysis.

In each muscle, DF decreased with length and each VA caused a dose-dependent decrease of DF at each length. The slope of absolute DF-length relationship decreased with increasing VA concentration. However, the slopes of relative values of DF vs length were never different from zero. The effects of VA were comparable to those of low $[Ca^{2+}]_o$.

The length dependence of DF is associated with a decrease of myofibrillar responsiveness to Ca^{2+} at shorter lengths (3-4). In this study H, E and I did not affect the relative impact on length on DF, so that H, E and I act mainly by reducing calcium availability to the myocardial contractile apparatus. (Supported by USPHS GM 36365, Mayo Foundation, and Saint-Luc Foundation, Belgium).

References
1. Rusy BF, Komai H: Anesthesiology 67:745-766, 1987
2. Housmans PR, Murat I: Anesthesiology 69:451-463, 1988
3. Allen DG, Kentish JC: J Mol Cell Cardiol. 17:821-840, 1985
4. Wang J, et al: Physiologist 32:218, 1989



S9

Title: EFFECTS OF HYPOTHERMIA ON NEUROLOGIC OUTCOME AND BRAIN GLUTAMATE LEVELS FOLLOWING ISCHEMIA IN RABBITS

Authors: AJ Baker, M.D., MH Zornow, M.D., MR Grafe, M.D., Ph.D., MS Scheller, M.D., TL Yaksh, Ph.D., *AA Larson, Ph.D., and HM Shapiro, M.D.
Affiliation: Dept. of Anesthesiology, UCSD, San Diego, CA and *Dept. of Veterinary Biology, U Minnesota, St. Paul, MN

Introduction: Moderate hypothermia has been repeatedly shown to be neuroprotective for episodes of transient cerebral ischemia (TCI). However, the mechanisms by which this protection is achieved are not fully understood. It is now known that excitatory amino acids (EAAs) are neurotoxic at concentrations found during TCI. The present study examined the relationship between brain tissue concentrations of these EAAs and neurologic outcome in normothermic (37°) and hypothermic (29°) rabbits subjected to 10 minutes of TCI.

Methods: Following approval by the Animal Care Committee, 10 rabbits were anesthetized and ventilated with halothane and oxygen. Femoral arterial and central venous catheters were inserted and a microdialysis catheter was placed into the dorsal hippocampus. Brain temperature was monitored with an epidural thermistor. Animals were then randomized to a normothermic (NT, 37°, N=5) or a hypothermic (HT, 29°, N=5) group. Ten minutes of TCI was produced using a neck tourniquet and systemic hypotension. Hippocampal microdialysate was collected prior to, during, and following the ischemic episode. The animals were scored for neurologic deficits at 24 and 48 hours following the TCI. The brains were then examined histologically for evidence of ischemic damage. Microdialysate was analyzed by HPLC for content of glutamate, aspartate and glycine. Neurologic and neuropathologic outcome were analyzed using a Mann-Whitney test. Amino acid levels were analyzed by ANOVA followed by Dunnett's test. Results with p values < 0.05 were considered significant.

Results: HT animals had better neurologic ($p<0.05$) and neuropathologic ($p<0.05$) outcomes than those in the NT group. Ischemia-induced increases in glutamate (Fig. 1), aspartate, and glycine levels were markedly attenuated in the HT group.

Discussion: This study confirms the often reported protective effects of moderate hypothermia on ischemic neuronal injury. The marked reductions in extracellular concentrations of glutamate, aspartate and glycine suggest that at least part of hypothermia's beneficial effects may be mediated through decreased release of these potentially neurotoxic amino acids.

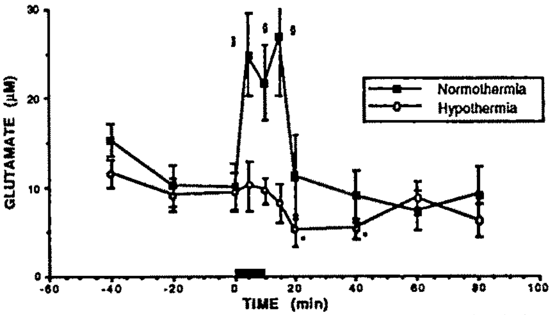


Figure 1. Glutamate concentrations (mean±SEM) in dialysate from hippocampus. Onset of 10 minutes of cerebral ischemia at t=0. Solid bar indicates duration of ischemia. § = $p<0.01$ and *=$p<0.05$ vs baseline.

S10

Title: SITE OF PRESSURE MEASUREMENT DURING CPAP: EFFECT ON CALCULATING IMPOSED WORK OF BREATHING

Authors: M.J. Banner, PhD; R.R. Kirby, MD; P.B. Blanch, RRT
Affiliation: Depts. of Anesth. and Physiol., Univ. of Fla., and Resp. Care Serv., Shands Hosp. at UF, Gainesville, FL 32610

Introduction. In calculating the imposed work of breathing during spontaneous ventilation with continuous positive airway pressure (CPAP), the usual method of measuring pressure at the Y piece of the breathing circuit might be less accurate than measuring at the distal (tracheal) end of the endotracheal tube (ETT); we compared the two methods.

Methods. Spontaneous breathing at 12 breaths/min was simulated with a piston-driven mechanical model with a tidal volume (V_T) of 0.5 L, peak sinusoidal inspiratory flow rate ($\dot{V}_I$) of 30 and 60 L/min, and inspiratory-to-expiratory ratio of 0.5. A continuous-flow (30 L/min) system (Emerson) provided CPAP at 10 cm H_2O through ETTs with an inner diameter (ID) of 6, 7, 8, or 9 mm. A pneumotachograph measured $\dot{V}_I$ and V_T. A transducer recorded pressure alternately at the Y piece of the breathing circuit and at the tracheal end of the ETT; these measurements were used to generate pressure-volume loops representing work imposed by the CPAP circuit alone (W_{CIR}) and by the CPAP circuit and the ETT, i.e., total apparatus work (W_{APP}), respectively. Data were analyzed with a 3-factor ANOVA and a Tukey multiple comparisons test; alpha was set at 0.5.

Results. W_{APP} was significantly greater than W_{CIR} at both $\dot{V}_I$s at each size of ETT. With the 6-mm-ID ETT, W_{APP} was 150% greater at $\dot{V}_I$ of 30 L/min and 127% greater at $\dot{V}_I$ of 60 L/min. W_{CIR} did not differ significantly between ETT sizes at 30 or at 60 L/min (Fig.)

Discussion. Airway pressure during CPAP should be measured at the tracheal end of the ETT to accurately assess work imposed by the entire breathing apparatus. Measuring pressure at the Y piece of the breathing circuit results in significant underestimation of pressure and work during CPAP, especially when the ETT has a small ID and $\dot{V}_I$ is high. Using an ETT with a built-in measuring lumen that terminates at the tracheal end is recommended.

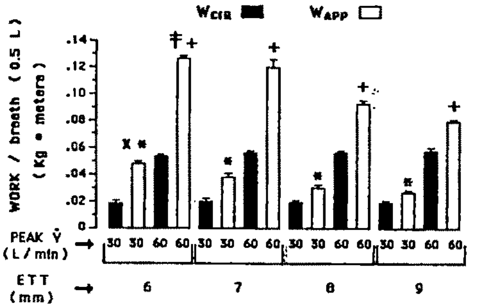


Figure. P < 0.05 compared with W_{CIR} at that size ETT at a flow rate of 30* and 60^+ L/min. P < 0.05 compared with other sizes of ETTs at peak flow rates of 30^X and $60^‡$ L/min. Abbreviations are defined in the text. Values are mean ± SD.

S11

TITLE: THORACOSCOPIC LASER ABLATION OF BULLOUS EMPHYSEMA: AN ANESTHETIC CASE STUDY

AUTHORS: SJ Barker, Ph.D., M.D., C Clarke, M.D., J Hyatt, N Le, C Bhakta, M.D.
AFFILIATION: Department of Anesthesiology, University of California, Irvine

Introduction. One-lung ventilation (OLV) for periods of roughly an hour is common practice during open thoracotomy for lung resection. Thoracoscopic laser ablation is a new procedure in which large pulmonary bullae are ablated by a CO2 laser through a thoracoscope. The chest is not opened, but the operative lung is deflated by intentional pneumothorax for periods exceeding three hours. We report here the first series of twelve patients who underwent this procedure. These patients were pulmonary cripples; their average preoperative FEV1 was 0.74 ± 0.77 liter. We describe the changes in all measured physiologic variables during and after OLV, the anesthetic technique tolerated best, and the perioperative anesthetic complications.

Methods. Each patient was monitored with a radial artery cannula, pulse oximeter, capnometer, transcutaneous PO2 and PCO2. Thermodilution pulmonary artery cannulas were inserted when indicated. Data were recorded from all monitors every five minutes. Arterial and mixed venous blood specimens were collected at frequent intervals for analysis. Oxygen consumption (VO2) was calculated from thermodilution cardiac output and blood gas data using the Fick equation. Mean and standard deviation values of all variables were calculated during both one and two-lung ventilation (TLV). The significance of any differences was determined by t-test. Balanced anesthesia consisted of oxygen, isoflurane, fentanyl, and vecuronium.

Results. All patients but one tolerated the anesthetic without hemodynamic instability. Table 1 shows the mean ± std. dev. of several measured variables during OLV and TLV. The average OLV time for each patient was 146 ± 50 min, while the average TLV time was 84 ± 39 min. The mean PaO2 fell from 387 ± 157 mmHg during TLV to 220 ± 112 mmHg during OLV. The PaCO2 changed little during OLV, but the PaCO2 - PETCO2 difference decreased (Table 1). Cardiac index was unchanged during OLV, but oxygen consumption index (VO2) rose slightly. Ten patients had significant airway leaks after the laser ablation, evidenced by expired tidal volumes at least 20% less than inspired. All required mechanical ventilation for more than 4 hours postoperatively. One patient died 14 days later from inspissated secretions and hypoxemia. The 11 survivors all feel subjectively better, and their average postoperative FEV1 is 1.06 ± 0.14 L (a 44% improvement). The average treadmill endurance has increased 48%.

Discussion. In view of the severity of their pulmonary disease, all patients tolerated OLV for long periods (up to 210 min) with surprisingly little difficulty. No one became seriously hypoxemic; the lowest arterial saturations were 88 - 90%. PaCO2 was well-controlled during OLV, but PaCO2 - PETCO2 increased, suggesting increased dead space. The most serious anesthetic problem was the management of the often large airway leak after return to TLV. The use of a high flow pressure-cycled ventilator (Siemens 900C) was of significant benefit in this regard. The air leaks resolved spontaneously within 21 days in all but one patient, who required an additional thoracoscopy. The success of this initial series implies that this new procedure may be a useful treatment of bullous emphysema. In this case, the use of OLV for periods approaching three hours will become commonplace.

Table 1. Mean ± (std. dev.) of variables during TLV and OLV.

	PaO2 mmHg	PaO2/PAO2	PaCO2 mmHg	PaCO2 - PETCO2	VO2 ml/min/m^2
TLV	387	0.59	44.0	3.6	91.2
(std.dev.)	(157)	(0.24)	(9.7)		(5.6)
OLV	220	0.39	45.1	7.7	111.1
(std.dev.)	(112)	(0.21)	(7.1)		(26.5)

S12

TITLE: IS THE HEMATOCRIT NEEDED PRIOR TO OUTPATIENT PEDIATRIC SURGERY?

AUTHORS: M.J. Baron, M.D., M.P.H., J.B. Gunter, M.D., P.F. White, Ph.D., M.D.
AFFILIATES: Dept. of Anesthesiology, Washington University, St. Louis, MO 63110

The usefulness of the preoperative hematocrit as a screening test prior to outpatient pediatric surgical procedures has been questioned[1]. It has been suggested that a careful history and physical examination are of greater importance than routine laboratory tests in determining a child's fitness for surgery. We evaluated the utility of the preoperative hematocrit as a screening test for surgical fitness in healthy children undergoing a variety of elective outpatient surgical procedures.

Methods: Using a retrospective study design, the age, type of surgical procedure, hematocrit, and reason for cancellation were obtained from the Same Day Surgery log books for 1863 consecutive pediatric outpatients scheduled for elective operations. Preoperative hematocrits (Hct) were performed using a finger stick technique and a microcapillary centrifuge. Hematocrit values were stratified by age and type of surgical procedure. Data were analyzed using ANOVA with Bartlett's test for equal variance and differences, p-values<0.05 were considered statistically significant.

Results: Mean hematocrit (± S.D.) varied with age (0-3 yr: 35.6 ± 3.0%; 3-5 yr: 37.1 ± 2.4%; 5-12 yr: 38.6 ± 2.6%; >12 yr: 40.4 ± 4.6%; p<0.001). Since the average age varies for different surgical procedures (table, p<0.001), hematocrit values will also vary depending on the surgical population. Only 28 (1.5%) scheduled operations were canceled. The most common reasons for cancellations on the day of surgery included upper respiratory infection (16), wheezing (3), fever of unknown origin (2), and failure to follow NPO instructions (4). Although 21 (1.1%) children had Hct values <30% or >50%, no child had a hematocrit sufficiently low or high to require a change in the anesthetic plan or cancellation of their operation.

OPERATION	N	AGE (YR)	MIN (MO)	MAX (YR)	HCT (%)	MIN (%)	MAX (%)
BMT	364	3.0 ± 2.9	0.2	14	36.3 ± 2.8	28	48
T & A	157	5.9 ± 3.1	0.8	18	37.3 ± 2.4	30	46
OTHER ENT	179	5.7 ± 4.0	0.1	16	37.5 ± 3.2	31	52
STRABISMUS	102	4.3 ± 3.9	0.2	18	37.4 ± 2.9	29	46
EUA	83	3.1 ± 3.2	0.1	13	36.7 ± 3.7	25	57
CAST CHANGE	10	3.8 ± 5.5	0.2	17	35.1 ± 3.3	31	40
BMT/A	72	4.9 ± 2.7	0.8	12	37.4 ± 2.7	33	48
X-RAY	16	1.9 ± 2.9	0.1	9	36.5 ± 3.3	32	45
HERNIA	192	2.4 ± 3.2	0.1	14	35.5 ± 3.8	26	60
ORTHOPED.	160	8.2 ± 5.0	0.1	18	38.4 ± 3.2	31	49
GENITOURIN.	173	4.2 ± 4.2	0.1	17	36.8 ± 3.1	28	49
PLASTIC	82	4.3 ± 5.0	0.1	18	36.9 ± 4.0	29	48
MISCELL.	273	6.2 ± 4.8	0.1	18	37.6 ± 3.8	25	50

Conclusions: Our data would question the value of a preoperative hematocrit in determining if a healthy appearing child is an acceptable candidate for outpatient anesthesia. Although it can be valuable as a general health screening tool[2], we would conclude that a preoperative hematocrit is not necessary for otherwise healthy children scheduled for elective outpatient operations.

References:

1. Roizen MF, et al. **Anesth Clin North Am** 1987;5:15.
2. O'Connor ME, et al. **Anesth Analg** 1990;70:176.

S13

Title: HEMODYNAMIC RESPONSES TO DESFLURANE (I653) ANESTHESIA: A COMPARISON WITH ISOFLURANE

Authors: RR Bartkowski MD PhD, SS Azad MD, TA Witkowski M.D., JL Seltzer MD, A Marr CRNA, J Lessin R.N.
Affiliation: Department of Anesthesiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107

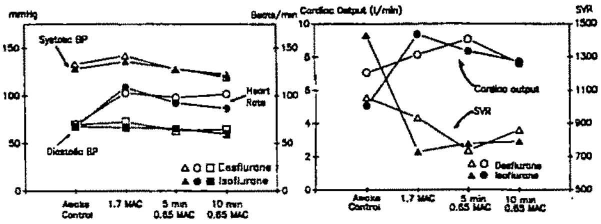
Introduction: Desflurane is a new inhalation anesthetic with low blood gas solubility (0.43) promising faster onset and recovery. It is similar in structure to isoflurane. The purpose of this study was to compare its hemodynamic responses to isoflurane in patients given anesthesia in a clinical setting.

Methods: Twenty-four patients gave informed consent to participate in this IRB approved study. Patients received midazolam 0.02-0.08 mg/kg i.v. 15-30 minutes prior to anesthesia. Anesthetic induction was accomplished with thiopental 4-8 mg/kg. Anesthesia was deepened to 1.7 MAC end tidal of either desflurane or isoflurane with N_2O/O_2 at a 60/40 ratio. Tracheal intubation was performed without muscle relaxation and patients were randomized to 0.65 MAC or 1.25 MAC (end tidal) of either agent with N_2O/O_2 in a 60/40 ratio. This concentration was held for 10 minutes. Measurements of systolic and diastolic pressure and heart rate were obtained from a Dinamap automated monitor while cardiac output was obtained from a non-invasive continuous doppler at the sternal notch (Lawrence Inc.). Hemodynamics were evaluated at the 1.7 MAC pre-intubation period and at 5 and 10 minutes of stable concentration. The data were analyze by repeated measures ANOVA with $p<0.05$ considered significant.

Results: Blood pressure and heart rate responses for the 0.65 MAC groups are shown in Figure 1. The heart rate increased significantly from pre-induction to all times when either agent was present. Systolic pressures were significantly higher in the desflurane group only at the pre-intubation point. Otherwise there were no differences between desflurane and isoflurane. Cardiac output was significantly elevated from control at all times after induction without differences between anesthetics. Systemic vascular resistance fell over the same time but did not achieve significance ($P=0.08$).

Discussion: The hemodynamic effects of anesthetics are an important part of their action. It is especially important to evaluate responses under clinical conditions i.e. premedicated patients having thiopental induction. Under these circumstances desflurane is associated with an increasing heart rate and increasing cardiac output. There is also a trend to vasodilation. In general desflurane is similar to isoflurane in its hemodynamic effects.

Figure 1. Cardiovascular Variables for Desflurane and Isoflurane during Anesthetic Induction.



S14

Title: DESFLURANE AND ALFENTANIL IN SURGICAL OUTPATIENTS: COMPARATIVE HEMODYNAMICS, EMERGENCE, AND RECOVERY

Authors: MF Battito, MD, R Langner, RN, EL Bradley, PhD
Affiliation: Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, Alabama

Desflurane (D), an inhalational anesthetic which is less soluble than nitrous oxide and currently in clinical trials, may play a significant role in providing anesthesia for outpatient surgery where quick return to street readiness is an important factor (1,2). This study in outpatient orthopedic surgical patients compares desflurane anesthesia *vs.* another commonly used anesthetic technique for outpatient surgery, alfentanil infusion (A).

Methods. After IRB approval and informed consent were obtained, 13 ASA I or II patients (ages 23-57 years old) scheduled for elective outpatient arthroscopic or peripheral orthopedic surgery were studied. Patients received premedication with Bicitra® 30 cc, p.o. For induction, both groups received intravenous alfentanil 15 µg/kg and thiopental 3-5 mg/kg to achieve unconsciousness. After endotracheal intubation, facilitated with succinylcholine, mechanical ventilation was provided ($ETCO_2$ 30-40 mm Hg) with 60% nitrous oxide in oxygen, and either desflurane inhalation (4-7%; $n=6$) or alfentanil infusion (1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $n=7$). Vecuronium was given as needed for neuromuscular paralysis. Desflurane concentration or alfentanil infusion rates were changed incrementally (5-20%) or alfentanil boluses were given as needed, based on anesthetic depth and hemodynamics. Mean arterial pressure (MAP) and heart rate (HR) were measured with a Dinamap 1846SX. Emergence times, recovery parameters, and adverse reactions were recorded.

Results. The groups were similar with respect to age, height, weight, sex, race, ASA status, and induction thiopental dose. One alfentanil patient was withdrawn from data analysis due to complications (intraoperative change in surgical procedure resulting in prolonged anesthesia time, high alfentanil dose, and postoperative respiratory depression). There were no significant differences in values of MAP and HR between the groups at specific times: preinduction, 2 min preincision, peak postincision, last OR value, first RR value. The mean duration of anesthesia was longer in group D (124 ± 28 SE min) than in group A patients (64 ± 16 min), but the difference did not reach a level of statistical significance. After discontinuing the anesthetic (from a minimum 10-min steady-state), the two groups were not statistically different in the time required to open eyes (5.0 ± 1.1 min for group A; 7.2 ± 1.2 for group D), squeeze hands on command (6.0 ± 1.1 min for group A; 7.7 ± 1.9 for group D), recite name and date of birth, tolerate fluids by mouth (71 ± 15 min for group A; 79 ± 26 for group D), sit, stand or walk (177 ± 34 min for group A; 150 ± 20 for group D). No one had intraoperative recall. Four of 6 patients in group A had nausea *vs.* 2 of 6 in group D ($P>0.05$). The groups were not statistically different for postoperative pain (verbal and visual), sedation, and Aldrete recovery scores.

Discussion. Hemodynamics, emergence, and recovery from desflurane *vs.* alfentanil anesthesia were not significantly different in this small group of outpatients. The relatively high incidence of nausea may be due to nitrous oxide or alfentanil administration in both groups. Desflurane provided safe anesthesia with rapid emergence and recovery in surgical outpatients.

This study was supported by a grant from Anaquest, Inc.

References: (1) *Anesth Analg* 70:3-7, 1990 (2) *Anesth Analg* 70:S378, 1990

S15

Title: COMPARISON OF PERIOPERATIVE ISCHEMIA TO ISCHEMIC ATTACKS IN NON-SURGICAL PATIENTS

Authors: W.S. Beattie, M.D., Ph.D., J.B. Forrest, M.B., D.N. Buckley, M.D.
Affiliation: Anaesthesia Department, McMaster University, Hamilton, Ontario, CANADA L8N 3Z5

Introduction: Perioperative infarction is a leading cause of morbidity and mortality in the post-operative period. Ischemia is a predictor of infarction. Most of the ischemia is asymptomatic, occurs post-operatively, and a percentage occurs without hemodynamic derangement.

Methods: After institutional ethics approval and informed consent, 45 patients had 24 hour ambulatory EKG recordings. Fifteen patients were non-surgical patients who had risk factors for ischemia and on no medication. Thirty patients had risk factors for coronary disease and were refered for non-cardiac surgery. Fifteen surgical patients had epidurals placed pre-operatively and had a combined epidural general technique and epidural morphine (dose .1 mg/kg) intraoperatively. Epidural patients were followed on the Ward and a dose of morphine adjusted to maintain VAS pain score to less than 2/10. Fifteen patients had general anaesthetic and parenteral narcotics for pain. Holter tapes were read by an independent blind observer using a Cardiodata Prodigy System. Ischemia was defined as ST segment depression of greater than 1 mm; 80 msec after the J point and having a duration of more than 1 min.

Results: Results are outlined in Table 1. Both surgical and nonsurgical groups displayed a circadian rhythm, each possessing an early morning peak. Most episodes were non-symptomatic. 7/22 S and 9/21 N/S were found to occur with no significant changes in HR. Ischemic episodes, which occured without HR changes (<10% increase), were significantly longer than HR mediated ischemic changes in both groups (P<.01).

When comparing the epidural to non-epidural surgical groups only, there were significantly fewer episodes of ischemia with epidural 14% vs 54%. This resulted from fewer tachycardia mediated ischemic episodes (1/4 ischemic episodes (EPI) vs 13/17 ischemic episodes (PAR)). There was no difference in the incidence or duration in non-HR mediated ischemia. One patient died of an acute MI who had had an epidural and 3 non-HR mediated ischemia episodes in the first 24 hrs post-operatively.

Table 1

COMPARISON OF ISCHEMIA BETWEEN SURGICAL & NON-SURGICAL MEAN ± STD

		ONSET HR	BASELINE HR	DURATION OF ISCHEMIA
NO CHANGE IN HR	S	79 ± 12	79 ± 11	27 ± 17
	N/S	60 ± 31	66 ± 1	67 ± 58
CHANGE IN HR	S	112 ± 21	90 ± 19	7 ± 5
	N/S	102 ± 13	75 ± 7	13 ± 11

Discussion: Post-operative ischemia is similar to the ischemia seen in non-surgical patients. HR mediated ischemia tends to be shorter duration. Epidural morphine reduces the frequency of HR mediated ischemia but not non-HR mediated ischemia. The data suggests non-HR medicated ischemia is an ominous event.

S16

Title: **PARENTAL UPSET CAUSED BY PARTICIPATING IN THEIR CHILD'S ANESTHETIC INDUCTION**

Authors: M. S. Bogetz, MD, J. A. Vessey, PhD, RNC, and C. L. Caserza, BSN, RN
Affiliation: Departments of Anesthesia, Physiological Nursing, and the UCSF Surgery Center, University of California, San Francisco 94143-0368

Introduction: Parental presence during their child's anesthetic induction continues to gain increasing acceptance as an important part of pediatric anesthesia and surgical care. Although their presence has been shown to be beneficial to the child (1,2), many parents become visibly upset during the induction process (3). This prospective, descriptive study was designed to determine what factors of the induction experience parents find upsetting and to identify those parents who are most likely to become upset.

Methods: With institutional approval, the study sample consisted of 93 mothers and 43 fathers whose children (n=103) were to undergo an inhalation induction without premedication for outpatient surgery. Children ranged in age from 1 to 11 years. Both parents were present for 32% of the inductions. Before induction, parent(s) supplied demographic and socioeconomic information. Then they were given detailed verbal information describing what to do and expect during the induction process. In addition, most parent(s) and children toured the induction room and played with the anesthesia mask and machine during their preoperative visit. Immediately after induction, parent(s) completed a 17 item survey which described child behaviors, parental concerns, staff behaviors, and environmental factors considered to be potentially upsetting to parent(s). A 4-point Likert scale ranging from "not upsetting" to "greatly upsetting" accompanied each item which was worded in the negative (e.g., "How upsetting did you find...?") to minimize the possibility that parents would only provide responses perceived as socially appropriate. Open-ended questions allowed parents to report other upsetting factors. In addition, two, 5-point rating scales were used by the anesthesiologist to describe the degree of parental participation and parental upset. The Pearson *r* correlation index was used to determine significant ($P < 0.05$) relationships.

Results: 93% of all fathers and 91% of all mothers reported some upset. However, mothers reported a significantly greater degree of upset than fathers ($P < 0.04$). The most upsetting factors were—separating from their child (mothers 69%; fathers 70%), watching and feeling their child go limp (mothers 60%; fathers 65%), seeing their child upset (mothers 59%; fathers 64%), being reminded of past experiences (mothers 31%; fathers 46%), not knowing what to do (mothers 22%; fathers 47%), and perceiving the induction process as rushed (mothers 25%; fathers 32%). Positive correlations were shown between the degree of reported upset and mothers who had one child ($P < 0.01$) and parents who were employed in health care ($P < 0.05$). Factors which did not correlate with upset included previous participation in an anesthetic induction, parental educational level, and the child's age. Importantly, there was poor correlation between the anesthesiologist's appraisal as to how upset a parent appeared and the parent's self-report. Content analysis of responses to the open-ended questions identified a sense of helplessness, lack of support, and hunger as additional areas of upset. Of note was that 40% of parents fasted with their children.

Discussion: Parental presence during a child's anesthetic induction is promoted as an excellent way to improve a child's cooperation and reduce the anxiety and stress of having to separate from a parent. However, these benefits may be at the emotional expense of the parents (3,4). Despite telling parents what to expect during an anesthetic induction and rehearsing the induction process with both parent and child, many parents report substantial upset. Insight into the factors which cause parental upset may help anesthesiologists, nurse anesthetists, nurses, and surgeons minimize parental upset while maintaining the benefits of parental presence for the child.

References:

1. Pediatrics 1967;39:1114.
2. Can Anaesth Soc J 1983;30:286.
3. Can J Anaesth 1990;37:177.
4. Anesthesiology 1988;69:A743.

S17

TITLE: Characteristics of Acute Respiratory Depression Seen With Epidural Fentanyl

AUTHOR: S.D. Bell, M.D.

AFFILIATION: Department of Anesthesiology
Jefferson Medical College
Thomas Jefferson University
Philadelphia, Pennsylvania

Introduction: Delayed respiratory depression with epidural fentanyl is extremely rare and usually associated with other events. Acute respiratory depression, however, is not uncommon[1]. Initially, most patients with epidural fentanyl were admitted to Intensive Care Units (ICU) and were closely monitored by various means. As the use of epidural narcotics has broadened to include its use on general surgical floors, there has not always been ready availability of monitors such as serial arterial blood gases, end tidal CO_2, pulse oximeters, or apne monitors. A retrospective evaluation of ventilatory parameters on patients with acute respiratory depression undergoing epidural fentanyl analgesia was performed to identify reliable markers of ventilatory depression.
Methods: 10 patients (who experienced acute respiratory depression) were evaluated in a retrospective manner. The degree of respiratory depression was determined by the amount of PCO_2 elevation as compared to baseline. Heart rate, respiratory rate, tidal volume, sedation, blood pressure, aggitation, and hemoglobin saturation were correlated with the PCO_2. Statistics were done with a P value of < 0.05, considered significant.
Results: There was no correlation between heart rate, blood pressure, aggitation or respiratory rate with PCO_2 elevation at any level which we observed. There was a statiscally significant decrease in arterial saturation from the patients baseline when the PCO_2 was > 54 torr. There was a significant correlation between sedation and fall in tidal volume at all levels of PCO_2.
Discussion: Contrary to that seen with intramuscularly administered narcotics, respiratory rate was not a reliable predictor of respiratory depression. Tidal volume, degree of sedation and arterial saturation (at higher PCO_2 levels) were positive predictors of respiratory depression.

Reference:

1.Cousins M: Anesthesiology 61:236-310, 1984

S18

TITLE: The Correlation Between Pulmonary Function and Resting and Dynamic Pain Scores in Post Aortic Surgery Patients

AUTHOR: S.D. Bell, M.D.

AFFILIATION: Department of Anesthesiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Introduction: Most studies which evaluate the adequacy of analgesia use pain measurement determinations which are obtained when the patient is lying quietly in bed.(1) This pain score may be very different from the score obtained when the patient is moving. We hypothesis that improvement in pulmonary function may correlate with active pain relief.

Methods: 16 patients ASA class III who had undergone aortic reconstructive surgery were evaluated retrospectively. Anesthesia consisted of O_2, N_2O, fentanyl, forane, muscle relaxation as needed. Group one consisted of eight patients who received continuous epidural fentanyl infusions for analgesia. Group two consisted of eight patients who received intravenous P.C.A. morphine either as their primary analgesic (N=6) or due to lack of adequate catheter function (N=2). Pain scores, FEV_1, and inspiratory force were obtained at rest and with activity breathing. Patients were orginally started on epidural fentanyl infusions of 70 mcg/hour. Patients who had pain on movement then had their infusion rates elevated incrementally to a maximum of 120-130 mcg/fentanyl per hour. P.C.A. were started at a continuous basal infusion rate of 1 mg of morphine per hour, with a bolus dose of 1 mg of morphine with a lockout time of ten minutes. With pain, the basal infusion rate was elevated incrementally to 2 mg of morphine per hour and the bolus dose was elevated to 2 mg of morphine with a maximum dose of 8 mg morphine per hour. Active pain control was defined as a visual analog pain score of less than 2.

Results: See Table 1

Discussion: Results showed that there was no significant difference in pulmonary function results with only resting pain control when one compared those patients receiving P.C.A. morphine to those with epidural fentanyl. Dynamic pain control was not achieved in the P.C.A. morphine group. There was a significant ($p < 0.05$) improvement in pulmonary function in those patients receiving epidural fentanyl who had dynamic pain relief.

Reference:

1. Cousins M: Anesthesiology 61:236-310,1984

Table 1

	Resting Pain Control		Increased Analgesia	
	FEV_1	Inspiratory Force	FEV_1	Inspiratory Force
Group 1 (Epidural)	34.1±6.2	24.7±6.1	60.8±7.1*	38.4±5.1*
			Active Pain Control	
Group 2 (PCA)	38.4±7.4	21.8±7	30.4±6.1	25.1±6.2
			No Active Pain Control	

*$p < 0.05$

S19

Title: Comparative effects of desflurane and isoflurane in the elderly

Authors: JA Bennett DDS MD, N Lingaraju MD, MM Keykhah MD, T McElrath BA, M Damask MD
Affiliation: Department of Anesthesiology, Hahnemann University, Phila, PA
Anaquest, Milburn, NJ.

Desflurane, a new inhaled anesthetic agent is considerably less soluble in blood and body tissues than other agents. The blood gas partition coefficient of desflurane is 0.42 compared with 1.4 for isoflurane.[1] Does it provide more rapid emergence and recovery from prolonged periods of anesthesia?

Methods: Following IRB approval 30 patients age ≥65, ASA class 2 or 3, consented to receive isoflurane or desflurane in a prospective randomized trial. Thiamylal 2 mg/kg and fentanyl 1-2µg/kg provided induction; succinylcholine facilitated intubation. Patients received isoflurane or desflurane in 60% N_2O/O_2, titrated to maintain heart rate and blood pressure within 20% of preinduction values. End tidal anesthetic concentrations were measured with a Datex infrared gas analyzer. Hemodynamic measurements occured every 2 min up until incision and then every 5 min. Time from discontinuation of all inhaled anesthetics to eye opening, hand grip on command, and subject's recall of name and date of birth were recorded. Time to fitness for discharge from the PACU was based on a modified Aldrete score.[2]

Results: Groups did not differ with respect to age, height, weight, dose of fentanyl, measurements of intraoperative hemodynamic stability. time to eye opening, hand grip, recall for birthdate and name, or the incidence of nausea and vomiting. The mean intraoperative anesthetic concentration was 0.64% (isoflurane) and 3.0% (desflurane). Mean PACU stay for the desflurane group was 44 min shorter than that of the isoflurane group (P<.04 Mann-Whitney U test).

Conclusion: Patients anesthetized with desflurane recover from anesthesia more quickly than patients receiving isoflurane.

TABLE 1	ISOFL N=16	DESFL N=14
ANES. TIME	191 ± 17	225 ± 14
EYES OPEN	7 ± 1.1	5 ± 0.9
HAND GRIP	9 ± 1.4	9 ± 1.4
NAME/DATE	14 ± 1.7	14 ± 1.9
PACU D/C	140 ± 19 *	96 ± 8 *

All values are Mean (min) ± S.E.M.
* P < 0.04

1.Eger EI. Anesth Analg 66:971-3 1987
2.Aldrete JA. Anesth Analg 43:924-33 1970

S20

TITLE: INTRATHECAL LIDOCAINE / FENTANYL INFUSION FOR POST-OPERATIVE ANALGESIA

AUTHORS: Brian K. Bevacqua, M.D., Alexey V. Slucky, M.D.

AFFILIATION: Anesthesia Section, VA Medical Center, Department of Anesthesiology, Case Western Reserve University
Cleveland, Ohio 44106

INTRODUCTION:

The continuation of catheter spinal anesthesia (CSA) into the post-operative period is a natural extension of its intra-operative use. While both intrathecal (IT) narcotics and local anesthetics alone have shown to provide analgesia, the potential synergy of a narcotic/local anesthetic infusion have not been explored. The present study reports the results of continuous IT infusions using combination lidocaine and fentanyl for post-operative analgesia.

METHODS:

Twenty (20) ASA three and four male patients (mean age 63, range 44-77 years) scheduled for twenty-one major vascular surgeries agreed to CSA. They were enrolled in the study following institutional review and informed consent. Nine patients had 18 gauge and twelve patients had 28 gauge IT catheters placed for CSA. Post-operatively, an IT infusion of 0.25% - 0.75% lidocaine with 2 ucg/cc fentanyl was initiated following the full return of motor function. The infusion volume (2-12 cc/hr) was individualized to the patient's analgesic requirements. All patients were monitored in the Surgical Intensive Care Unit and allowed free access to parenteral morphine for analgesia. Both the patient's and nurses' evaluation of post-operative pain was recorded (on a scale of excellent/good/fair/poor).

RESULTS:

The mean duration of infusion was 42 hours (range 25-97 hrs). Eight patients underwent intra-abdominal procedures while twelve had peripheral procedures. The patients had infusions established at the following lidocaine concentrations 0.25% (n=7), 0.33% (n=5), 0.5% (n=5), and 0.75% (n=2); all containing 2 ucg/cc of fentanyl. Sixteen of nineteen patients (84%) reported good or excellent analgesia. Two patients with 0.25% and one patient with 0.75% lidocaine infusions (all peripheral surgeries) were dissatisfied with their analgesia. A sensory and/or motor level was observed at all lidocaine concentrations, but the neurologic effects were independent of lidocaine concentration.

There were no instances of respiratory depression or hemodynamic instability attributed to the IT infusions. One post-operative headache which resolved with conservative therapy was noted. Two instances of lower extremity hypoesthesia and motor weakness were seen after the IT catheters were inadvertently removed while the patients were anticoagulated. Both cases resolved spontaneously with no permanent neurological sequelae. One patient expired five days after an emergent repair of a ruptured thoracoabdominal aneurysm.

DISCUSSION:

Regional anesthesia continued into the post-operative period provides excellent analgesia and may decrease morbidity by providing improved ablation of "surgical stress"[1]. While epidural analgesia remains the more popular technique, IT lidocaine infusions have been shown to be effective for post-operative analgesia[2]. Intrathecal infusion markedly reduces local anesthetic requirements without increasing untoward effects, thus offering an additional safety factor when compared to epidural analgesia. The addition of fentanyl increased the incidence of motor and sensory impairment without increasing analgesia. Hence, the addition of fentanyl to IT lidocaine infusion does not seem to offer advantages over lidocaine alone in our patient population.

REFERENCES:

1. Anesthesiology, 1987, 66: 729-736

2. Anesthesiology, 9/90 (in press)

S21

Title: REVERSAL OF DEEP NEUROMUSCULAR BLOCKADE WITH LOW DOSE NEOSTIGMINE IN INFANTS AND CHILDREN

Authors: J. Bires, M.D., D. McGregor, M.D., R. Lennon, D.O.
Affiliation: Department of Anesthesiology, Mayo Clinic,
Rochester, MN 55905

Introduction. Standard texts of pediatric anesthesia vary greatly in the recommended dose of neostigmine required to antagonize neuromuscular blockade. These recommendations range from 40-70 µg/kg. Particularly in small infants, where there is the potential for respiratory inadequacy from residual neuromuscular blockade, the reversal dose of neostigmine chosen has usually been at the higher end of the recommended range. In this study, we attempted reversal from deep neuromuscular blockade in infants and children with low dose neostigmine (40 µg/kg).

Methods. With IRB approval, forty pediatric patients, ages 2 mo to 8 y, physical status I or II, were studied. Anesthetic induction and maintenance were accomplished with 30% O_2, 70% N_2O, and halothane. Neuromuscular function was monitored with a Puritan-Bennett relaxograph. T_1 % of control and the T_4/T_1 ratio were followed. Intubation was performed after relaxation with atracurium or vecuronium. A continuous infusion of relaxant was titrated to keep one twitch present with $T_1 < 10\%$ of control. At the completion of surgery, the infusion of muscle relaxant was discontinued and neuromuscular blockade reversed with 20 µg/kg atropine and 40 µg/kg neostigmine. Reversal was deemed to be adequate when the T_4/T_1 ratio exceeded 70%, and extubation was accomplished at this time if clinical criteria for extubation were present.

Results. Results are summarized as follows:

Neuro-muscular Relaxant	# patients	Age	Reversal Time (minutes) mean ± SEM
Atrucurium	10	2-12 mo	5.7 ± 0.7*
	10	13 mo - 8 y	8.3 ± 0.6*†
Vecuronium	10	2-12 mo	7.0 ± 0.5
	10	13 mo - 7 y	6.3 ± 0.6†

* *$p < 0.02$ by unpaired two-tailed t-test*
† *$p < 0.05$ by unpaired two-tailed t-test*

Discussion. In this study, all patients had adequate reversal of neuromuscular blockade with 40 µg/kg of neostigmine as measured by EMG as well as clinical criteria. Despite the routine use of higher dose neostigmine for reversal of neuromuscular blockade in infants in order to ensure that residual blockade does not cause respiratory embarrassment, we found no respiratory compromise in the infants in this study who received a reversal dose of 40 µg/kg neostigmine. Our findings are in agreement with others who suggest that neostigmine dose requirements are smaller in infants and children when compared with adults.[1] We suggest that 40 µg/kg neostigmine is adequate for reversal of deep neuromuscular blockade induced by atracurium or vecuronium in infants and children, provided there is also careful monitoring of the neuromuscular junction.

Reference. 1. Anesthesiology 59:220-225, 1983.

S22

Title: ESMOLOL IS SUPERIOR TO NITROPRUSSIDE FOR CONTROLLED HYPOTENSION DURING ORAL SURGERY

Authors: WS Blau, MD, PhD, ER Kafer, MD,
JA Anderson, MD, DDS

Affiliation: Department of Anesthesiology, University
of North Carolina, Chapel Hill 27599-7010

Introduction. Controlled hypotension is employed during LeFort osteotomies in order to minimize blood loss and optimize surgical conditions following down-fracture of the maxilla. Although the use of sodium nitroprusside (SNP) for controlled hypotension is well established, consistent evidence that blood loss is reduced is lacking. The ultrashort acting beta blocker esmolol (ESM) can be used as an adjunct for SNP-induced hypotension or as a primary drug for hypotension. The present study was designed to compare 1) the efficacy of ESM and SNP as primary drugs for reducing blood pressure during oral surgery, and 2) their effects on blood loss.

Methods. After institutional approval and individual informed consent, 15 ASA-1 patients, ages 15-30, underwent LeFort osteotomies with SNP (n=9) or ESM (n=6) as the primary hypotensive drug. Subjects were randomly assigned to receive either ESM (500 µg/kg bolus every 2-4 min as necessary, titrate maintenance infusion from 100-300 $\mu g.kg^{-1}.min^{-1}$) or SNP (0.5-5.0 $\mu g.kg^{-1}.min^{-1}$ titrated) infusions to reduce the mean arterial pressure (MAP) to 55-65 mmHg beginning with the down-fracture of the maxilla. Conventional anesthetic (1.0% isoflurane, 65% N_2O) and monitoring (arterial cannula) techniques were used. Hemodynamic data were obtained at two-minute intervals during the hypotensive period, for statistical analysis. Estimates of total blood loss were based on volumetric assessment of the irrigation solution used and fluid/blood aspirated from the surgical field.

Results. The mean duration of hypotension was 95 min (range 50-155 min) and the average infusion rates for SNP and ESM were 1.6 and 177 $\mu g.kg^{-1}.min^{-1}$, respectively. Although both drugs were efficacious in reducing blood pressure to the target range, both the MAP and the variability were greater for SNP (table). The blood loss in the SNP group was 85% greater than in the ESM group. There were no complications, and all patients were discharged on the second postoperative day.

Discussion. Both SNP and ESM are effective for inducing controlled hypotension; however, the choice of drug can influence outcome: ESM provided a more stable MAP with reduced blood loss. In the overall strategy of patient management, including blood conservation, ESM offered a major advantage over SNP.

TREATMENT	MAP* (mmHg)	STANDARD DEVIATION OF MAP*	BLOOD LOSS(ml)
SNP (n=9)	63.4±0.6	11.2±0.9	784±78
ESM (n=6)	58.5±0.9	7.1±0.5	423±88
P value	<0.001	<0.01	<0.01

*Means and standard deviations of MAP are based on repeat 2 min observations for each patient during hypotension. MEANS ± SE.

S23

Title: 2,3 BUTANEDIONE MONOXIME IMPROVES FUNCTION AND RHYTHM AFTER HYPOPERFUSION IN ISOLATED GUINEA PIG HEARTS

Authors: M Boban, MD, DF Stowe, MD, PhD, AH Goldberg, MD, PhD, N Buljubasic, MD, JP Kampine, MD, PhD, and ZJ Bosnjak, PhD
Affiliation: Depts. of Anesthesiology and Physiology, Medical College of Wisconsin, Milwaukee, WI 53226

2,3 butanedione monoxime (BDM) is a very effective uncoupler of the excitation-contraction process[1] which could be useful as an adjunct for cardioplegic solutions.[2] Our aim was to determine whether BDM has a protective effect on improving cardiac function and reducing the development of dysrhythmias following severe hypoperfusion.

After institutional approval, 20 guinea pig hearts were isolated and perfused by the Langendorff technique at a control perfusion pressure (PP) of 55 torr with modified Krebs-Ringer solution at 36.5°C. Bipolar recording electrodes were placed in the right atrium and ventricle to monitor rhythm and a balloon was placed in the left ventricle to measure left ventricular pressure (LVP). In 10 hearts, 5 mM BDM was given for 10 min before, during, and 10 min after hypoperfusion at zero PP; 10 control hearts received no BDM. The duration of hypoperfusion was 30 min; this was followed by 40 min of reperfusion at control PP. Statistical differences were analyzed by ANOVA (means ± SEM).

BDM significantly decreased the duration of ventricular fibrillation (VF) and premature ventricular excitations (PVE) during reperfusion following hypoperfusion at zero PP (fig. 1). In 2 of 10 control hearts and 9 of 10 BDM treated hearts VF spontaneously converted to sinus rhythm within 2 min. BDM decreased LVP to 40% of control prior to and 10 min after hypoperfusion. LVP recovery 40 min later with reperfusion (fig.2) was significantly higher in the BDM group (81±5% of control) compared to the control group (57±4% of control).

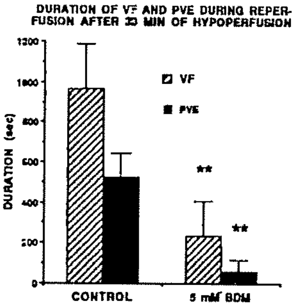


Figure 1

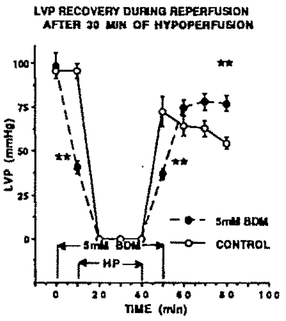


Figure 2

** $p<0.02$ vs CONTROL

Although the mechanism of action for the negative inotropic action of BDM is not yet clear, a major effector site is likely the contractile apparatus.[1,3] This study indicates that BDM protects the heart against dysrhythmias and functional damage occurring during hypoperfusion and reperfusion. BDM may prove useful in preventing the "stunned myocardium" syndrome or as an additive to cardioplegic solutions for cardiac surgery. (Supported by NIH grant HL 34708)

References: 1) *Pflugers Arch* 416:219, 1990; 2) *Circ Res* 65: 1441, 1989; 3) *FASEB J* 4:A560.,1990

S24

Title: **Blood Loss During Liver Transplantation: 1984-1990**

Authors: C. Boucaud, M.D., J.L. Lichtor, M.D., J. Emond, M.D., C. Broelsch, M.D., Ph.D., J. Erickson, M.D., S. Polk, M.D., G. Rupani, M.D.
Affiliation: Departments of Anesthesia & Critical Care and Surgery, The University of Chicago, Chicago, IL

Introduction: Orthotopic liver transplantation for children and adults has been performed at our hospital since 1984. Blood loss during this procedure can be excessive. We sought to determine the preoperative factors that correlate significantly with blood usage.

Methods: After the approval of our clinical investigation committee, we reviewed the records of 179 children (age ≤ 15 yr) and 179 adults who underwent liver transplantion from November 1984 to May 1990. Preoperative factors considered included chronicity of disease, history of previous abdominal surgery, previous bleeding, encephalopathy, magnitude of ascites, history of previous transplant, transplant number, PT, PTT, platelet count, creatinine, albumin, and bilirubin. Time in the operating room was also recorded. Dependent factors included amount of banked blood transfused, normalized to equivalent blood volumes. Multiple linear regression analysis was used to determine the most significant preoperative factors for blood loss.

Results: **Children.** The average age was 3.9 years. The diagnoses of the patients included biliary atresia (n=87) and chronic active hepatitis (n=11). The average amount of blood administered was 2.0 blood volumes. Multiple linear regression analysis (regression coefficient in parentheses) revealed that age (b=-0.14), previous bleeding (b=1.10), OR time (b=0.26), and encephalopathy (b=0.75) correlated with blood loss.

Adults. The average age was 42.1 years. The diagnoses of the patients included chronic active hepatitis (n=57) and cryptogenic cirrhosis (n=25). The average amount of blood administered was 2.5 blood volumes. Multiple linear regression analysis revealed that OR time (b=0.42), magnitude of ascites (b=1.19), and year of transplant (b=-0.44) correlated positively with blood loss.

Discussion: For both adults and children, as expected, OR time correlated positively with blood loss. As experience improved, blood loss also decreased in adults. In children, why younger patients required more blood is not clear, although this factor was also found significant in a previous report.[1] Generally, the younger the patient requiring a transplant, the sicker the patient, and the segment sites of these patients generate greater blood loss. In children, previous bleeding and encephalopathy are associated with portal hypertension and the gravity of the patient's disease, making need for blood more expected. In adults, ascites is also associated with portal hypertension. Interestingly, the preoperative coagulation screen did not correlate with blood usage, which agrees with the findings of other studies.[2] The use of autologous washed blood did not correlate with blood usage. Blood use was 30% less than that cited in previous studies, and transplant number did not specifically correlate with blood usage. Further work is necessary to determine if the use of such techniques as thromboelastography will decrease blood utilization.

References:

1. Anesthesiology 68:607-611, 1988.
2. Transplantation Proceedings 21:3533-3534, 1989.

S25

Title: **Thromboelastography During Liver Transplantation: Does Blood Loss Correlate with Abnormalities?**

Authors: C. Boucaud, M.D., J.L. Lichtor, M.D., J. Erickson, M.D., S. Polk, M.D., G. Rupani, M.D., J. Emond, M.D., C. Broelsch, M.D., Ph.D
Affiliation: The Departments of Anesthesia and Critical Care and Surgery, The University of Chicago, Chicago, IL

Introduction: Earlier studies have demonstrated that severe coagulopathies are present during liver transplantation.[1] That they occur suggests that were thromboelastography (TEG) to be used during liver transplantation, blood loss might be reduced and appropriate factor replacement therapy initiated. In this study, we sought to correlate blood product utilization with TEG findings in patients with cirrhosis undergoing liver transplanation.

Methods: The study was approved by our clinical investigation committee. Blood replacement was guided by Hct (maintained above 22). Administration of fresh frozen plasma was guided by evidence of continual oozing and if persistent, by the administration of platelets. We performed TEG four times on 9 patients (5 adults and 4 children) during the transplantation procedure: after induction of anesthesia (baseline), 20 to 30 min into the anhepatic phase, 20 to 25 min after reperfusion of the graft, and at the end of the surgery. pH, ionized calcium, and Hct were measured each time and the amount of blood products administered was recorded. From the TEG recording, the following variables were calculated: R (time from placement of blood in the cuvette until an amplitude of 1 mm was reached, i.e., the time to initial fibrin formation); K (time from end of R to the time an amplitude of 20 mm was reached, reflecting the rapidity of fibrin building and fibrin cross-linking); MA (maximal amplitude measuring the strength of the fibrin clot, which depends on platelet number and function and fibrinogen level). Quantification of clot lysis was made by measuring A_{60}:MA. The anesthesiologist caring for the patient was blinded to TEG findings.

Results: The table illustrates the TEG variables calculated at different times and the amount of blood, fresh frozen plasma, and platelets administered from one measurement time to another. Regression analysis showed that the amount of blood, FFP, or platelets used did not correlate with TEG variables; blood pH, Ca, and temperature also did not correlate significantly with TEG variables or with blood products administered. Even when TEG clotting variables were quite severe, the amount of blood, FFP, and platelets administered was very low.

Discussion: Despite severe clotting abnormalities during liver transplantation, we found that TEG was not useful to the clinician for determination of appropriate blood and blood factor replacement in the operative field.

Reference: Anesth Analg 64:888-896, 1985

TABLE I

	> Induction	Anhepathy	Reperfusion	End
R (mm)	44,3(14.5-97)	73(17-250)	>200(86->300)	76.4(22-200)
K (mm)	15.3(2-38)	10.1(5-20)	56(34-79)	18.8(11-36)
MA (mm)	56(42-65)	56(50-65)		57.5(48-77)
A60:MA(mm)	0.95(0.91-1)	0.85(0.25-1)		0.97(0.92-1)
PH	7.41(7.35-7.54)	7.37(7.27-7.46)	7.25(7.21-7.32)	7.31(7.22-7.39)
Ionized calcium	1.1(1-1.8)	0.88(0.43-1.11)	1.04(0.82-1.5)	0.93(0.66-1.3)
Temperature	36.3(34-38)	34.5(33-37)	33.5(32-36)	34.3(33-36)
Hct	0.30(0.25-0.34)	0.28(0.24-0.34)	0.30(0.22-0.36)	0.28(0.22-0.35)
BVAd	0.01(0-0.12)	0.13(0-0.34)	0.23(0-0.81)	0.4(0-1.36)
FFP (ml/Kg)	2.2(0-13.6)	23.3(0-79)	36.7(0-105)	54.7(0-158)
Platelet (ml/Kg)	0	0	0	0.22(0-2)

S26

Title: **Aminophylline Accelerates Recovery from Fatigue in Rat Isolated Diaphragm by Acting on Adenosine Receptors**

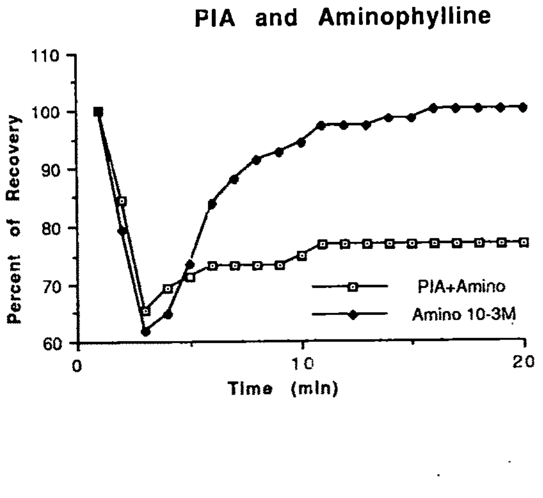
Authors: C Boucaud, MD, A Polk, BS, S Glusman, MD, PhD
Affiliation: Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL

Introduction: Fatigue of respiratory muscles is a significant contributor to the pathophysiology of respiratory failure, although the mechanism of respiratory muscle fatigue has yet to be elucidated. Adenosine has been shown to increase in the perfusate from fatigued muscles and to regulate adenylate cyclase activity by acting on two functionally distinct adenosine receptors and on a non-receptor site, the P-site. Adenosine deaminase, the adenosine degradative enzyme, accelerates recovery from fatigue in the isolated rat diaphragm, an action similar to that of aminophylline, a methylxanthine with adenosine antagonist properties. We examined the role of adenosine receptors and the P-site on the mechanism of recovery from fatigue in the isolated rat diaphragm.

Method: After approval by the Animal Care Committee, Sprague-Dawley rats were anesthetized and a strip of diaphragm was removed. The costal margin of the diaphragm was fixed to the floor of a perfusion chamber while the tendon was connected to a force transducer. The preparation was continuously perfused with modified Ringer's solution aereated with 95% oxygen, 5% CO_2. The diaphragm was supramaximally stimulated with bipolar field electrodes at 0.1 Hz. To induce fatigue, the frequency of stimulation was increased to 1.0 Hz for 3 min. Recovery from fatigue was studied by analyzing the time course of return of twitch tension to baseline values after return to 0.1 Hz.

Results: Aminophylline or the theophylline analogue 8-phenyltheophylline (8-PT) increased twitch tension that the isolated rat diaphragm generated when stimulated at 0.1 Hz and greatly accelerated recovery in the fatigued muscle. Adenosine or 2-phenyl-isopropyl-adenosine (PIA), an adenosine analogue with adenosine receptor agonist properties with no activity at the P-site, did not affect the increase in twitch tension induced by aminophylline or 8-PT but blocked, in a dose-related manner, the acceleration in recovery from fatigue induced by the xanthines (fig). Verapamil, a calcium channel blocker, blocked the increase in twitch tension produced by aminophylline and 8-PT without affecting the rate of recovery from fatigue.

Discussion: Methylxanthines have two effects on isolated rat diaphragm: increase in twitch tension and acceleration of recovery from fatigue. These two effects of the xanthines do not share a common mechanism. The increase in twitch tension seems to be related to changes in calcium conductance through voltage dependent calcium channels since it is selectively blocked by calcium channel blockers. Recovery from fatigue by the xanthines is not affected by the presence of calcium channel blockers but is blocked by adenosine and the adenosine analogue PIA. The dose-dependent reversal by adenosine and PIA of the effect of the xanthines on fatigue, suggests a competitive interaction at the adenosine receptor level and not at the P-site. By prolonging recovery from fatigue, adenosine may play the role of a local modulator protecting the muscle from energy depletion associated with overactivity.



S27

TITLE: INCREASED ANALGESIA REQUIREMENTS IN PATIENTS USING PCA NARCOTICS FOR POST OPERATIVE ANALGESIA

AUTHORS: M.C. Brody, M.D., D.S. Wheeler, M.D., B.R. Stacey, M.D., D.F. Burke, M.D., C. Dunwoody, R.N.
AFFILIATION: Pain Evaluation and Treatment Institute, Department of Anesthesiology, University of Pittsburgh, Pittsburgh, PA 15213

Introduction: Patient controlled analgesia (PCA) has proven to be an effective modality for post-operative pain control. Programmable parameters on PCA devices ensure safety by limiting the dosage administered during a given time interval while allowing flexibility in the dosage schedule.

We questioned, however, how often the maximum allowable settings on our PCA devices (4 hour limit - 30 cc or 30 mg "morphine equivalents") were exceeded by a patient to achieve effective analgesia and what characteristics defined the patient populations requiring supplemental analgesics (i.e., continuous infusion) in addition to the PCA.

Methods: Clinical records are routinely maintained by our Acute Pain Service (APS), which include patient demographics, type of surgery, analgesia requirements, efficacy of pain control and medication related side effects. After reviewing our own APS records from the past 13 months, we obtained permission from our institutional medical records committee to review the charts of patients who consumed more than 50 mg "morphine equivalents" during any 8 hour shift.

Results: Review of the analgesia requirements of 1,167 orthopedic, general, vascular and urologic surgery patients using PCA for post-operative pain control revealed that 31 (2.66%) patients used more than 50 mg of morphine (or equal analgesic dose of Dilaudid or Demerol) per 8 hour shift. Of these patients, 61.3% were using regular opioid medication preoperatively with evidence of tolerance, and 19.4% of patients reported chronic benzodiazepam use or were identified as having active alcohol abuse. Further, 38.7% were victims of severe multiple orthopedic trauma. Fisher exact tests indicated that only preoperative evidence of tolerance and multiple orthopedic trauma measures were significantly associated ($P < .02$).

Thirty percent of the 31 patients reported inadequate analgesia despite using "high" doses of opioid. None of these patients, however, experienced clinically significant sedation or respiratory depression.

Discussion: Patients rarely require more than the maximum allowable dosage that can be provided by the Abbott PCA device. In our experience, the most common reason for exceeding the 4 hour limit is programmer error or selecting an inappropriately low setting. In our sample, opioid tolerance from chronic use was the most common patient characteristic leading to increased post-operative requirements.

Large doses of opioid can be administered to tolerant patients without unacceptable risk of respiratory depression or sedation so that effective analgesia can be achieved. It is important to recognize, however, that those patients requiring higher dosages of opioid for effective pain control may be at risk for an abstinence syndrome based on preoperative tolerance to opioids or other psychoactive substances.

S28

TITLE: COMPARISON OF CRYSTALLINE SKIN TEMPERATURE TO ESOPHAGEAL, PULMONARY ARTERY, AND BLADDER TEMPERATURES DURING CARDIOPULMONARY BYPASS

AUTHORS: S.J. Brull, M.D., N.R. Connelly, M.D., D.G. Silverman, M.D.
AFFILIATION: Anes. Dept., Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

Introduction: Liquid crystal thermometry has long been in use; however, it has not been found to be an accurate indication of core temperature.[1] The present study sought to compare crystalline temperature (CT) to esophageal (ET), pulmonary artery (PA), and bladder (BT) temperatures during the periods of rapid temperature change on cardiopulmonary bypass (CPB).

Methods: Following IRB approval, CT, ET, PA, and BT were compared in 8 patients undergoing CPB. Prior to institution of CPB, ET, PA, and BT were monitored as per usual clinical practice, and a CT strip (Sharn, Tampa, FL) was placed on the patient's forehead. During the first 10 min of cooling and the first 10 min of re-warming, all 4 temperatures were recorded at 1 min intervals. The difference between CT and each of the other parameters over time was analyzed by Wilcoxon signed rank test; $p<0.05$ was considered to be significant.

Results: During cooling, CT maintained a close relationship with BT, consistently reading within 1°C (p=ns for change in CT-BT over the 10 min cooling period). The relationship between CT and BT was also maintained during rewarming. Similar consistency was noted for CT-ET and CT-PA during the warming period (i.e., there was a significant difference over time for CT-PA and CT-ET during cooling). Alternatively, the relationships between CT and ET and between CT and PA were inconsistent during the cooling period. This may be attributable to more marked lowering of the ET and PA temperature readings by direct application of iced slush.

Discussion: The data suggest that CT correlates with other means of temperature assessment during periods of rapid cooling and warming, so long as a given technique is not altered by direct application of a cooling or warming solution. During warming in the present study, such extraneous factors were avoided, and the average mean differences between CT-BT, CT-ET, and CT-PA were only 0.3°C, 0.5°C, and 1.0°C, respectively. Such high correlation should facilitate the interchange of readily available, inexpensive and noninvasive means of temperature monitoring.

References

1. Anaesthesia 39:54-56, 1984

	COOLING			WARMING		
	CT-ET	CT-PA	CT-BT	CT-ET	CT-PA	CT-BT
MINS.						
1	0.7	0.7	-0.3	0.1	-1.1	-0.8
2	0.7	1.4	-0.2	-0.2	-1.2	-0.6
3	1.1	2.3	-0.1	-0.4	-1.2	-0.5
4	1.7	3.0	0.2	-0.5	-1.3	-0.3
5	1.8	3.6	0.4	-0.8	-0.7	-0.1
6	1.8	4.2	0.7	-0.8	-0.7	-0.1
7	1.7	4.1	0.2	-0.8	-0.9	0.0
8	2.0	5.5	0.6	-0.8	-0.9	-0.2
9	2.5	4.9	0.7	-0.8	-1.1	0.3
10	2.9	4.4	0.6	-1.0	-1.2	0.5

S29

TITLE: ILIAC CREST WOUND PERFUSION FOR POSTOPERATIVE ANALGESIA

AUTHORS: S.J. Brull, M.D., J. Lieponis, M.D., M. Murphy, M.D., D.G. Silverman, M.D.
AFFILIATION: Depts. of Anesthesiology and Orthopedics, Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

Introduction: Although wound perfusion with local anesthetics through an indwelling catheter was first described in 1935, it was used rarely in the clinical setting until the past decade, when its benefit following cholecystectomy and splenectomy was documented.[1,2] Following orthopedic vertebral decompression and fusion with bone grafting, the operative site associated with most discomfort often is the donor site (i.e., iliac crest). The pain following bone graft harvesting should be particularly well-suited to the indwelling catheter technique of analgesia, because of its severe intensity and localized nature. However, there are no studies that have evaluated the effectiveness of local anesthetic wound perfusion for postoperative skeletal pain. This study evaluated, by means of visual analog scale (VAS) scoring system, the effectiveness of intermittent 0.25% bupivacaine infusion.

Methods: Following institutional investigational committee approval, 8 patients who had undergone vertebral fusion with bone grafting were evaluated. In all cases, the iliac crest served as the patient's donor site. Prior to surgical closure, an indwelling 20 ga. bullet-tip 3 hole radiopaque nylon catheter (Kendall Co., Boston, MA) was introduced percutaneously by the orthopedic surgeon. All patients received general endotracheal anesthesia with 70% nitrous oxide in oxygen and isoflurane end tidal 0.5-2.0%. Postoperatively, when the patient first complained of iliac crest pain, a 10-cm VAS score was obtained. The VAS scale was anchored with 0 as no pain and 10 as the worst pain imaginable. The indwelling catheter then was injected with 10 cc of 0.25% bupivacaine with 1:200,000 epinephrine. Fifteen min later, the VAS pain score was reassessed and patient satisfaction (0=none, 10=complete) was quantified. Data are expressed as medians and ranges, and were analyzed with Wilcoxon signed rank test. For all analyses, $p<0.05$ was considered statistically significant.

Results: As noted in the table, in all cases, the infusion of local anesthetic via the indwelling catheter resulted in lowering of the VAS scores. Overall, the VAS scores decreased from a preinjection median value of 6.8 (range 3-9) to a median value of 1.0 (range 0-4). The median satisfaction score was 10.0 (range 9-10). There were no instances of adverse local anesthetic reactions or wound complications.

Discussion: The present data suggest that infusion of a local anesthetic appears to be an effective method of providing analgesia following harvesting of iliac crest bone graft. This effectiveness was evidenced by both a marked decline in VAS pain scores after local anesthetic infusion, as well as the superior VAS satisfaction scores achieved.

References

1. Surg Gynecol Obstet 157:338, 1983
2. Br J Anaesth 58:615-619, 1986

TABLE

VAS PRE	VAS POST	VAS SATISFACTION
8.0	2.0	10.0
9.0	0.0	9.0
8.0	1.0	10.0
3.0	1.0	10.0
5.0	1.0	10.0
5.5	4.0	10.0
5.0	1.0	10.0
8.0	4.0	10.0

S30

Title: EFFECTS OF ENFLURANE ON GLOBAL ISCHEMIA AND REPERFUSION IN ISOLATED GUINEA PIG HEARTS

Authors: N Buljubasic MD, J Marijic MD, M Boban, MD, DF Stowe MD PhD, ZJ Bosnjak, PhD
Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

Cardiac function can be severely compromised during temporary ischemia resulting from tissue hypoperfusion (HP). Volatile anesthetics have generated interest as agents which may reduce myocardial damage and the incidence and duration of severe dysrhythmias during ischemia and reperfusion (RP). We know that in isolated hearts, halothane (HAL) produces a decrease in calcium accumulation following regional[1] and global ischemia and reperfusion and dramatically improves cardiac function following global hypoxia.[2] This study examines the effects of enflurane (ENF) on functional recovery, incidence and duration of arrhythmias following global HP.

After institutional approval, the hearts (n=32) were isolated and perfused at control perfusion pressure (PP) (55 torr) with Krebs-Ringer solution. Heart rate (HR), atrio-ventricular conduction time (AVCT), left ventricular pressure, coronary inflow and outflow PO_2, for MVO_2 calculation, were measured. Hearts were divided into four groups: Groups 1 and 2 were perfused at 0% and groups 3 and 4 at 25% of the initial PP for 30 min followed by 40 min of RP at 55 torr. In groups 2 and 4 ENF (3.3%) (1±0.05 mM) was given 10 min prior to, during, and 10 minutes following HP. Statistical differences were determined by one-way ANOVA and Chi-square tests. Data are means±SEM.

ENF decreased heart rate 15% (control 219±6 bpm); MVO_2 22% (control 54±12 µl/min/g); systolic LVP 41% (control 96±7 torr). During HP, systolic LVP and heart rate decreased and AV time progressively increased; AV block and atrial and ventricular dysrhythmias occurred in all hearts. Predominant dysrhythmias during HP were 2° and 3° AV block and atrial and ventricular bradydysrhythmias which progressed to atrial and/or ventricular arrest during 0% PP. At the beginning of RP, systolic LVP increased up to 71 and 85% of control in Groups 1 and 3 and then gradually declined to 61 and 76% at 40 min of RP. There was no decline in pressure during RP in Groups 2 and 4 where systolic pressure was steadily increasing to 63 and 91% of initial control. During RP MVO_2 returned to control level. At 30 min after discontinuation of ENF there was no difference in systolic or diastolic LVP between groups with same PP exept higher systolic LVP in group 4 than group 3 (Figure 2). After 0 and 25% PP (groups 1 and 2) the incidences of ventricular fibrillation (VF) were 100% and 0%, respectively. ENF did not affect this variable.

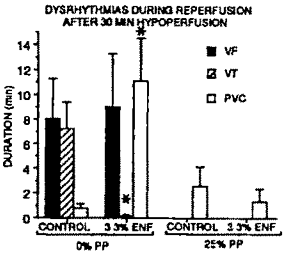


Figure 1

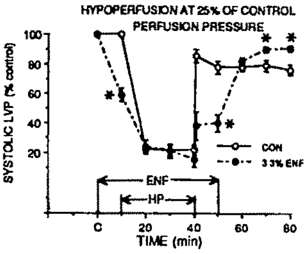


Figure 2

* $p<0.05$ vs Control

Results of this study suggest that ENF facilitates recovery of contractile function following 25% but not after 0% PP. ENF also decreases duration of VT during RP following 0% HP but at the same time increases the incidence and duration of PVC (Figure 1). *In vitro*, ENF offers partial protection against hypoperfusion induced decrease in contractility, and only when coronary flow is maintained, possibly by reducing energy requirements before, during and after HP and reducing calcium accumulation known to occur during reperfusion.

References: 1) *Anesthesiology* 67:197, 1987
2) *Anesthesiology* 69:A30, 1988

S31

A COMPARISON OF MORPHINE AND BUPRENORPHINE VIA P.C.A. PLUS BASAL INFUSION IN POSTCESAREAN DELIVERY PATIENTS

Capogna G, Celleno D, Costantino P, Sebastiani M, Muratori F, Cipriani G.

Dpt of Anesthesia, Fatebenefratelli General Hospital
ROME, ITALY

INTRODUCTION. Recently a combination of PCA plus a continuous IV infusion of an opioid analgesic agents has been introduced for postoperative analgesia (1-3) This randomized, double blind study was undertaken to compare the analgesic efficacy and adverse effects of morphine and buprenorphine administered via patient controlled analgesia (PCA) plus basal infusion (BI) in postcesarean delivery patients.

METHODS. Forty patients who gave informed consent, received a basal infusion of either morphine(M) 1mg/h (n=20) or buprenorphine(B) 0.03mg/h (n=20) plus PCA. The PCA system was set to deliver a bolus of either M 1mg or B 0.03 mg, with a lockout interval of 10 and 15 min respectively. A loading dose of 5 mg of M or 0.15 mg of B was given if necessary before starting the BI. Quality of analgesia and side effects, assessed by a visual analogue scale(VAS) and by a subjective scale were noted. Statistical analysis was performed by Student's t-test and Mann Whitney U-test.

RESULTS. Mean(SD) duration of BI was 969.0(298.8) and 1075(211.0) min in M and B respectively. Total M dose was 25.5(6.1)mg and total B dose was 0.71(0.2)mg. Hourly dose was 0.63mg/h for M and 0.04mg/h for B. No changes in vital signs nor differences in quality of analgesia and incidence of side effects were observed between the groups.
The mean B:M potency ratio was 32:1. Patients receiving B had a more prolonged postinfusion analgesia - 34.2(12.8) vs 284.1(70.3) min ($p < 0.01$) - and a significant improvement of sedation score.

DISCUSSION. This therapy offered an excellent level of analgesia. Buprenorphine appears to be useful when a prolonged analgesia after the end of the BI is required.

REFERENCES.
1. Sinatra R et Al; Anesthesiology 1989;71:502-507
2. Owen H et Al.Anaesthesia 1989;44:11-13
3. Mc Kenzie. Anesthesiology 1988;69:1027

Table 1: side effects(n. of patients)

	Morphine	Buprenorphine
Analgesia less than 3VAS	1	1
nausea	4	6
vomiting	2	3
pruritus	2	5
somnolence	6	16

S32

Title: ROLE OF TRANSSARCOLEMMAL Ca^{2+} ENTRY IN THE NEGATIVE INOTROPIC EFFECT OF NITROUS OXIDE IN ISOLATED FERRET VENTRICULAR MYOCARDIUM

Authors: E.G. Carton, M.D. and P.R. Housmans, M.D., Ph.D.
Affiliation: Dept. Anesth. and Pharmacol., Mayo Foundation, Rochester, MN 55905

Introduction. Nitrous oxide (N_2O) decreases myocardial contractility in isolated mammalian ventricular muscle by reducing intracellular Ca^{2+} availability with no effect on myofibrillar Ca^{2+} responsiveness (1). In order to further define its site of action, we assessed the effect of N_2O on transsarcolemmal Ca^{2+} influx in ventricular muscle where the release of Ca^{2+} from the sarcoplasmic reticulum was inhibited by the plant alkaloid, ryanodine.

Methods. After institutional approval, we studied nine ferret right ventricular papillary muscles in a HEPES-buffered physiological salt solution (pH 7.3-7.4; 30°C; 4 s stimulus interval; $[Ca^{2+}]_o$ 2.25 mM). Peak developed force (DF) was measured in isometric twitches after equilibration in: 1) 50% N_2-50% O_2; 2) 50% N_2O-50% O_2; 3) 50% N_2-50% O_2. This sequence was repeated in the presence of 1 μM ryanodine. Values of DF (mean ± SD) in N_2O were compared to the mean of those in 50% N_2 (immediately before and after exposure to N_2O), with Student's paired t-test.

Results. 50% N_2O caused a significant reduction in DF (15.56 ± 7.49 $mN.mm^{-2}$ in 50% N_2O compared to 18.38 ± 9.38 $mN.mm^{-2}$ in 50% N_2, $p < 0.01$) (Figure, left). In 1 μM ryanodine, 50% N_2O caused a further significant decrease in DF (2.32 ± 1.55 $mN.mm^{-2}$ in 50% N_2O compared to 3.56 ± 2.35 $mN.mm^{-2}$ in 50% N_2, $p < 0.01$) (Figure, right).

Discussion. The N_2O-induced decrease in intracellular Ca^{2+} availability results from a decreased transsarcolemmal Ca^{2+} influx and/or a decreased release of Ca^{2+} from the sarcoplasmic reticulum. The decrease in force by N_2O in the presence of ryanodine suggests that at least part of the negative inotropic effect of N_2O is due to an inhibition of Ca^{2+} entry through the sarcolemma.

Supported by NIH GM 36365 and Mayo Foundation.

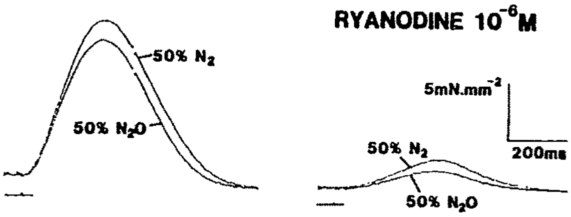


Figure: Isometric twitches (50% N_2-50% O_2 and 50% N_2O-50% O_2 without (left) and with (right) ryanodine 10^{-6}M.

Reference
1. Carton, E.G., Wanek, L.A., Housmans, P.R.: Anesthesiology, in press, 1990.

S33

TITLE: AMBULATORY PCA - A NEW APPROACH TO POSTOPERATIVE PAIN MANAGEMENT

AUTHORS: L.H. Chandler, M.D., P.F. White, Ph.D., M.D.
AFFILIATION: Departments of Anesthesiology, Alaska Surgery Center, Anchorage AK and Washington University, St. Louis, MO 63110

With the continued growth in ambulatory surgery, the ability to provide adequate pain relief has assumed increased importance. Inadequate management of postoperative pain remains one of the most common reasons for unanticipated admissions after outpatient surgery. In this preliminary study, we evaluated the use of patient-controlled analgesia (PCA) after major orthopedic procedures performed on an ambulatory basis.

90 healthy, consenting ASA I-II outpatients, ages 18-66 yrs, undergoing either anterior cruciate ligament repair or shoulder reconstruction procedures were allowed to self-administer morphine sulfate using an ambulatory PCA device according to an IRB-approved protocol. Following discharge from the outpatient facility, all patients received a continuous "basal" infusion consisting of morphine, 1-2 mg/h, which could be supplemented with 1-1.5 mg bolus doses on demand. In addition to determining the opioid dosage requirements, we recorded side effects and reasons for discontinuing PCA therapy. We also evaluated the effect of age, ASA physical status, and smoking history on the postoperative analgesic requirement.

The mean (± S.D.) morphine dosage requirement and total number of self-administered bolus doses are summarized as a function of age in table 1. Neither age, smoking history, nor ASA physical status significantly altered the opioid requirement. The average patient used the PCA pump for 1.8 ± 0.6 days. The most common reasons for prematurely discontinuing PCA therapy (<48 h) included: persistent nausea and vomiting (n = 12), inability to void (n = 2), and intravenous (iv) catheter infiltration (n = 2). In addition, nine other patients had to have their iv restarted to continue PCA therapy. Transient nausea (35%), pruritus (9%), vomiting (5%), and inability to void (4%) were the most common side effects. Although 10-20% of the patients reported occasional moderate-to-severe levels of pain after discharge from the outpatient facility, all patients were highly satisfied with their PCA therapy. Patients began physical therapy 16±15 days after their operation and returned to work in 52±35 days.

In summary, conventional intravenous PCA techniques can effectively control pain after ambulatory surgery. The use of a simplified analgesic delivery system (e.g. subcutaneous PCA) would alleviate problems associated with iv catheter infiltration. Further studies are needed to determine the role of PCA therapy in the outpatient setting.

Table 1: Postoperative PCA dosage requirements

Age range (yrs)	Ave. morphine usage (mg/hr)	Bolus doses (n) 0-24h	Bolus doses (n) 24-48h
18 - 30 (n = 35)	2.0 ± 0.2	14 ± 9	8 ± 9
31 - 49 (n = 45)	2.8 ± 0.3	18 ± 12	8 ± 8
50 - 66 (n = 10)	1.8 ± 0.5	10 ± 8	3 ± 4

S34

TITLE: CHANGES IN END-TIDAL CO$_2$ WITH BRONCHIAL OCCLUSION AND ONE LUNG CANINE VENTILATION

AUTHORS: P. Chang, M.D., D. Johnson, M.D., T. Hurst, M.Vet.Sc, B. Reynolds, M.D., S. Lang, M.D., I. Mayers, M.D.
AFFILIATION: Departments of Anaesthesia and Medicine, University of Saskatchewan, Saskatoon, Canada S7N 0X0

Accidental endobronchial intubation is a common anesthetic complication. We studied the utility of end-tidal CO$_2$ (E_TCO_2) in the immediate detection of endobronchial intubation in mechanically ventilated dogs. The experimental protocol followed university guidelines. Six dogs were instrumented and left pulmonary artery (P.A.) flow was estimated using an external flow probe. A Fogerty catheter was positioned under bronchoscopic guidance in the left mainstem bronchus. Following left bronchial occlusion, left P.A. flow and E_TCO_2 were measured at 0, 1, 3 and 5 minutes. We randomly occluded the bronchus in each dog under baseline conditions, after insufflation with .8% halothane, and with simultaneous clamping of the left P.A.. * denotes significance compared to 0 minutes by paired t-test ($p < .05$)

Minutes	0	1	3	5
	Baseline Group			
E_T CO$_2$	35 ± 4	30* ± 5	33 ± 6	35 ± 4
Flow	770 ±533	828 ±569	637 ±375	575* ±306
	Halothane Group			
E_T CO$_2$	31 ± 5	25* ± 4	31 ± 6	32 ± 5
Flow	495 ±127	507 ±162	480 ±213	383* ±178
	P.A. Occlusion Group			
E_T CO$_2$	35 ± 7	35 ± 7	35 ± 7	35 ± 7
Flow	607 ±238	0	0	0

E_TCO_2 significantly decreased after 1 minute of bronchial occlusion with or without halothane. This transient change was obliterated after 5 minutes corresponding to a significant decrease in left P.A. flow. After simultaneous mechanical occlusion of left P.A., flow diversion is immediate and no decrease in E_TCO_2 was observed. The small and transient decrease in E_TCO_2 limit its utility as a monitor of accidental endobronchial intubation.

MEDICIN LIBRARY

S35

Title: EPIDURAL ANALGESIA, INSTRUMENTAL VAGINAL DELIVERY AND THE PRIMIPAROUS PARTURIENT

Authors: RC Chantigian, M.D., DR Danilenko-Dixon, M.D.
Affiliation: Departments of Anesthesia and Obstetrics, Mayo Clinic, Rochester, MN

Introduction: Lumbar epidural analgesia (LEA) has been associated with a 2-5 fold increase in instrumental vaginal deliveries. But is LEA being selected in patients who may be destined to an operative delivery? Factors associated with the selection of LEA in primiparous women undergoing vaginal delivery were reviewed. In addition, factors which may be associated with instrumental vaginal delivery including LEA were reviewed.

Methods: With IRB approval, 1014 consecutive primiparous vaginal deliveries of liveborn, singleton, vertex presentation newborns > 32 weeks EGA delivered in 1987-88 were included in this study. Multivariable analyses with logistic regression coefficients were determined for variables that may be associated with instrumental deliveries.

Results: LEA was chosen in 58% of these patients. Instrumental deliveries occurred in 44% of patients with LEA and in 16% of patients without LEA.

Significant factors (P value < 0.05) in choosing LEA included higher socioeconomic status, greater EGA, larger newborns, less cervical dilation on admission, prolonged latent phase, prolonged active phase of labor, use of pitocin, and choice of an obstetrician vs. family physician. Women with LEA had a longer second stage of labor. No significance was noted with maternal age in choosing LEA. Newborn outcome as determined by Apgar scores and blood gas pH was similar whether LEA was used or not.

A logistic regression model revealed the following factors associated with instrumental vaginal deliveries in order of significance: duration of the active phase, socioeconomic status, epidural analgesia, induction with an unripe cervix, prolonged latent phase, choice of OB vs. FM, cervical dilation on admission.

Conclusions: Parturients who received LEA had some factors suggestive of more difficult labors. Many of the variables which are associated with the choice of LEA for labor are also associated with the need for instrumental delivery. Patients of obstetricians select LEA more often than patients of family physicians, and women of higher socioeconomic status were also more likely to choose epidural anesthesia. Newborn outcome was no different.

Three factors accounted for nearly 50% of the variance for instrumental deliveries (in order of importance): duration of the active phase, socioeconomic status,and use of LEA.

S36

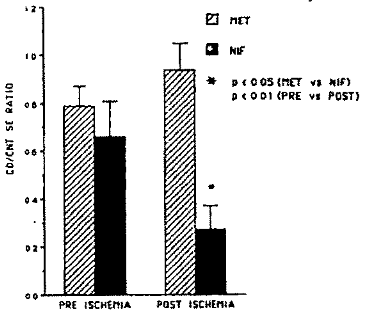
TITLE: EFFECTS OF METOPROLOL AND NIFEDIPINE ON POST-ISCHEMIA REGIONAL MYOCARDIAL BLOOD FLOW IN A CHRONIC SWINE MODEL

AUTHORS: D.C.H. Cheng, FRCPC; C.M. Feindel, FRCSC; J. Cruz, M.D.; P. Boylen, BSc.; D. Ong, M.D.;
AFFILIATION: Anaes. and Surgery Depts., Toronto Western Division, The Toronto Hospital, University of Toronto, Toronto, Ontario, Canada M5T 2S8

Introduction: Beta adrenergic blockers have been shown to lower the incidence of perioperative myocardial ischemia in patients (1). This study compared the effects of metoprolol and nifedipine on post-ischemia regional myocardial blood flow in a swine model of collateralized coronary vessels, under isoflurane anesthesia at a constant coronary perfusion pressure.

Methods: After institutional approval, eight piglets between 6-8 kg were operated via a left thoracotomy. The left anterior descending coronary artery (LAD) was banded to induce collateral vessels. After ten weeks, the pigs (approx. 30 kg) were anesthetized with isoflurane/oxygen with controlled ventilation. The constriction band on the LAD was identified and ligated to ensure total occlusion. Coronary perfusion pressure (DBP minus LVEDP) was maintained at 40 mmHg. Baseline coronary blood flow (CBF) was determined by Sn-113 microspheres injected via the left atrium. The pigs were randomized to receive either metoprolol (10 ug/kg/min) or nifedipine (5 ug/kg/min) infusion for 20 min. At the same CPP, the circumflex coronary artery that supplied the collateral vessels was occluded for 30 sec. The post-ischemia CBF was measured immediately by Ce-141 microspheres injection. Using triphenyl tetrazolium chloride staining, the collateral dependent zone (CD) was identified distal to the LAD occlusion and the control zone (CNT) distal to the circumflex artery.

Results: Nifedipine, but not metoprolol, caused a significant decrease in post-ischemia CBF in subendocardial (SE) and epicardial (EPI) regions at CD zone. Intercoronary (CD/CNT) blood flow in SE region was significantly lower in the nifedipine group (Figure).



Discussion: Since nifedipine causes intercoronary steal, metoprolol appears to be a safer drug to use during ischemia under isoflurane anesthesia in a chronic swine model with collateralized coronary vessels.

This study was supported in part by the David Sheridan Research Award.

Reference

1. Anesthesiology 69:343-347, 1988

S37

Title: ANESTHETIC DRUGS AND NONANESTHESIOLOGISTS

Authors: E.Y. Cheng, M.D., J.P. Kampine, M.D., Ph.D.
Affiliation: Dept. of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI, 53226

Introduction Many drugs administered primarily by anesthesiologists in the operating room are utilized in many other areas of the hospital by nonanesthesiologists. One of these areas is the Emergency Department (ED). This study examined 1) the use of intravenous anesthetics, nitrous oxide, and muscle relaxants by the ED, 2) who supervises the use of these drugs, and 3) how patients are monitored during their use.

Methods Surveys inquiring about the use of anesthetics (ultrashort acting barbiturates, nitrous oxide), muscle relaxants (depolarizing and nondepolarizing), monitoring, and supervision were sent to all EDs of hospitals with 300 or more beds in Wisconsin (WI) and Illinois (IL). The data were examined by state.

Results There was a 53% response rate. Muscle relaxants were the most frequently used, followed by nitrous oxide and intravenous anesthetics in both IL and WI (Fig. 1). The ED or the ED with the hospital credential committee or hospital pharmacy is responsible for ensuring that these drugs are used appropriately 58.2% of the time. Approximately 9.2% of the time, the use of these drugs was under the supervision of the Anesthesiology Department (Fig. 2). There was no official supervision in 12.2% of the hospitals that used these agents. Other responses (20.4%) were placed in a miscellaneous category. When anesthetics or muscle relaxants were given, cardiac (31 of 39 respondents), oximetry (27 of 39), and blood pressure monitors (17 of 39) were most frequently used (Fig. 3). Twenty-eight respondents used more than one type of monitoring.

Discussion This data shows that anesthetic agents are frequently used in the ED without input from the Anesthesiology Department or respiratory monitoring. This can have a potential adverse effect on patient care. Both the American Board of Anesthesiologists and the Joint Commission of Accredited Hospital Organization recommend that anesthesiologists help develop standards of care and monitor the quality of anesthetic care throughout the hospital. By becoming involved with establishing the quality of anesthesia wherever it is given in the hospital, we will hopefully improve the quality of patient care as well as help protect the professional interests of anesthesiologists.

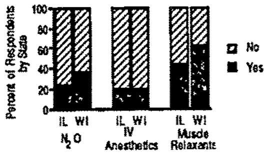


Fig. 1. Percent of EDs using N_2O, IV anesthetics, and muscle relaxants.

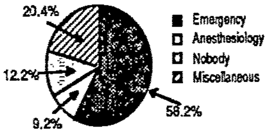


Fig. 2. Supervision of anesthetic agents used by EDs.

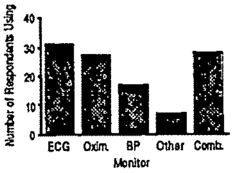


Fig. 3. Monitors used by 39 EDs during administration of anesthetics or muscle relaxants.

S38

Title: A COMPARISON OF RETROBULBAR AND GENERAL ANESTHESIA FOR STRABISMUS SURGERY

Authors: K. Cheng MD, A. Biglan MD, C. Larson MD*, J.D'Antonio PhD
Affiliation: Departments of Ophthalmology and Anesthesiology*, Eye and Ear Hospital, Pgh., PA

Introduction: The present study was undertaken to compare post-op morbidity of retrobulbar anesthesia with that of general anesthesia for monocular strabismus surgery.

Methods: With approval from the Human Research Committee, a prospective randomized controlled study was undertaken. Patients were randomly selected to receive either general anesthesia (GA) or retrobulbar blockade/IV sedation (RB) for planned strabismus surgery. The patients were ASA I or II teenagers or adults, fasting and unpremedicated. The GA patients received IV fentanyl, thiopental, and succinylcholine; then were intubated and maintained on $N2O/O2/$ isoflurane. The RB group received midazolam/ fentanyl IV sedation, then retrobulbar block using 2% mepivacaine with hyaluronidase. The administration of antiemetics was limited to use in the post-op period for protracted or severe vomiting. Each patient was evaluated and given a score every 30 minutes for the first 90 minutes post-op in the following categories: nausea/vomiting (1=feeling well, 2=upset stomach, 3=vomiting x 1, 4=vomiting x 2, 5=vomiting x 3); post-operative eye pain (1=no discomfort, 2=mild discomfort, 3=moderate discomfort - no analgesics, 4=moderate discomfort relieved with acetaminophen, 5=severe pain); and activity level (1=normal activity, 2=decreased stamina, 3=not feeling well, and 4=confined to bedrest). The scores were totaled for the 3 time periods and compared between the GA and RB groups using Student's t-test. The times from the completion of surgery to discharge from the same day surgery unit were also recorded and compared.

Results: Score totals are summarized below with data expressed as means ± S.D.

	Retrobulbar (n=31)	General (n=30)
N/V	3.3 ± 0.7	3.8 ± 2.1
Pain	4.9 ± 1.8	5.8 ± 1.7
Activity	5.9 ± 2.0*	8.6 ± 3.2
Discharge Time	140 ± 84 min*	279 ± 88 min

(* $p<0.05$ compared with GA group)

Discussion: Retrobulbar block with IV sedation for monocular strabismus surgery was associated with better activity levels during the early post-operative period and significantly earlier discharge times from a same day surgery unit when compared to a general anesthesia group. Nausea/vomiting and post-op eye pain were not significantly different between the two anesthetic groups in the early post-operative period.

S39

Title: CLONIDINE IMPROVES NEUROLOGIC OUTCOME FOLLOWING INCOMPLETE ISCHEMIA IN RATS.

Authors: M.A. Cheng, M.D., W.E. Hoffman, Ph.D., D.J. Miletich, Ph.D., R.F. Albrecht, M.D.
Affiliation: University of Illinois-Chicago/Michael Reese Hospital, Chicago, Illinois

Introduction: Central sympathetic activity and circulating catecholamines may play a deleterious role in ischemic brain injury. The α2 agonist clonidine inhibits central catecholamine release. In these experiments, we investigated neurologic outcome, brain histopathology, circulating catecholamines and plasma glucose following incomplete ischemia in rats pretreated with clonidine.

Methods: Following approval by the Institutional Animal Care Committee, male Sprague-Dawley rats 350-450 g were anesthetized, endotracheally intubated, and ventilated with 2% isoflurane in room air. Catheters for continuous BP monitoring, blood gas, glucose and catecholamine sampling, and drug administration were inserted in one femoral artery and vein. The right jugular vein was catheterized for blood withdrawal. The right common carotid was isolated for later clamping. Isoflurane was then withdrawn and control anesthesia maintained with 25 μg/kg/hr fentanyl and 70% N_2O in oxygen. Rats were randomly assigned to 2 groups: Group 1 (n=10) was given no pretreatment; Group 2 was pretreated with clonidine (10 μg/kg) 30 min before ischemia. Cerebral ischemia was produced for 30 minutes by right carotid occlusion and hemorrhagic hypotension with MAP maintained at 35 mmHg ± 2 mmHg. Temperature was maintained at 37°C, $PaCO_2$ at 35 - 40 mmHg, and pH at 7.40. Plasma glucose was measured before, during and after ischemia. Plasma catecholamines were measured by radioenzymatic assay at the end of ischemic period. After 30 minutes of ischemia, the carotid was unclamped and the withdrawn blood was reinfused. Catheters were removed, incisions were closed, and the trachea extubated. Neurologic outcome was assessed by a blinded evaluator for a 3 day period, beginning 24 hr post-ischemia using an 18 point deficit score. Basic histopathology was evaluated with light microscopy by a blinded neuropathologist using a 9 point scale.

Results: Clonidine treated rats had an increase in blood pressure to 140-150 mmHg which decreased to a hypotensive response (80 mmHg) before ischemia (controls = 110 mmHg). Before ischemia, plasma glucose was 230 mg/100 ml in clonidine treated rats, higher than in controls (167 mg/100 ml), $P<0.05$). Plasma norepinephrine and epinephrine were lower in clonidine treated compared to control rats at the end of ischemia. Neurologic outcome and neuropathology were significantly improved in clonidine pretreated rats ($P<0.05$).

Discussion: These results show that clonidine pretreatment improves neurologic outcome following incomplete ischemia. The mechanism appears to be a decrease in plasma or brain catecholamine activity. An increase in blood glucose in the clonidine treated group should have worsened outcome by increasing ischemia brain lactate production.

S40

Title: MASS SPECTROSCOPIC/GAS CHROMATOGRAPH ANALYSIS OF DRUG COMBINATIONS FOR REGIONAL ANESTHESIA

Authors: J. M. Christie, M.D., C. W. Jones, Ph.D.

Affiliation: Department of Anesthesiology, University of South Florida College of Medicine, Tampa, FL and V.A. Medical Center, Bay Pines, FL 33504

Introduction: Anesthesiologists routinely administer opiates, adrenergic agonists, and local anesthetics alone or in combination for perioperative and cancer pain.[1-3] Basic information about the properties and interactions of these agents is lacking or inadequate. This study examined a variety of drugs that could be used with synergism in the intrathecal or epidural space. The purpose of the work was to define the chemical stability of the agents in combination, and therefore to make recommendations about the safety of such combinations for clinical practice.

Methods: Duramorph, fentanyl, lidocaine, bupivacaine, phenylephrine, clonidine, and ketamine were examined. All possible combinations were evaluated by mass spectroscopy to determine if original structures remained intact. Standards for spectral peaks were established for each drug and then for each drug combination. Drugs and drug combinations were extracted by liquid-liquid extraction using Toxi-A tubes; the organic phases were evaporated under a nitrogen atmosphere; and the residues reconstituted with 25 microliters of methanol, prior to injection. All drugs were separated by capillary gas chromatography utilizing a 0.2mm x 12mm methylsilicone column; and analyzed by electron-impact mass spectrometry utilizing a Hewlett-Packard 5970 mass selective detector.

Results: All possible combinations of the seven drugs were analyzed using mass spectroscopy. Spectral peaks were stable under all conditions. No evidence of change in chemical structure and no generation of novel chemical species were found with any drug combination.

Discussion: Combinations of drugs of different classes may be advantageous for epidural or intrathecal administration. Drug manufacturers currently use gross evidence of instability to determine drug-drug incompatibility (ie, color change or precipitation). Mass spectroscopy provides analysis of chemical structure and definitively identifies drug incompatibility. We used mass spectroscopy to determine the chemical stability of drug combinations for potential use in regional anesthesia. We conclude that the formulations tested are stable when combined without any evidence of change in structure. These agents may therefore be mixed in the same syringe or infusion sets to permit ease of titration or administration. Other toxicities of regional drug administration may occur; however, this analysis excludes drug-drug interaction as factor for the agents studied.

References:
1. Anesthesiology 61:276-310, 1984.
2. Anesthesiology 71:640-646, 1989.
3. Anesthesiology 71:535-540, 1989.

S41

Title: WORK OF BREATHING AND PRESSURE SUPPORT VENTILATION DURING GENERAL ANESTHESIA

Authors: J.M. Christie, M.D., M. Leon, M.D.

Affiliation: Department of Anesthesiology, University of South Florida College of Medicine, Tampa, Florida 33612 and VA Medical Center, Bay Pines, Florida 33504

Introduction: General anesthesia reduces functional residual capacity, decreases respiratory system compliance, and increases elastic and resistive inspiratory work (W_I). Spontaneous breathing may prove inadequate under such conditions. Pressure support ventilation (PSV) provides a specified level of pressure during spontaneous inspiration and theoretically should reduce W_I. PSV may be a useful alternative to conventional intraoperative mechanical ventilation. We compared the W_I in anesthetized patients who were breathing with a conventional circle system, a demand flow circuit and PSV.

Methods: After Institutional Review Board approval, ten consenting patients who were undergoing combined inhalation-regional anesthesia were studied. A Siemens 900D Anesthesia/Ventilator System provided PSV (5 cm H_2O) or demand gas flow during spontaneous inspiration. Gas flow during demand breathing and PSV was initiated when inspiration caused a $\Delta \leq 1.0$ cm H_2O in airway pressure. A Drager Narkomed 3 or Ohmeda Modulus II Plus provided a gas flow rate of 6 L/min through a standard anesthesia circle system. Airway pressure (P_{AW}), gas flow rate, and esophageal pressure (P_{ES}) were continuously transduced and signaled to a computer. Tidal volume (V_T) and respiratory rate (RR) were computed from the flow curve. W_I was calculated as the integral of the area enclosed by the plot of P_{ES} and lung volume during inspiration. Heart rate (HR) and mean arterial pressure (MAP) were recorded, and arterial blood was obtained for gas tension and pH analysis. Data are summarized as mean ± SD and were statistically compared with an analysis of variance.

Results: No differences were found in arterial pH, PCO_2 and PO_2, V_T, or RR between the three modes of ventilation. W_I was significantly more reduced by PSV than by the demand valve and circle system (Table). Mean P_{AW} was significantly higher while patients were breathing during PSV than with the demand or circle systems. No significant alterations in HR or MAP were noted at any time. FiO_2 was maintained constant (0.5±.05).

	Circle	Demand	PSV
RR (/min)	16±4	16±5	15±5
V_T (ml)	358±101	352±90	371±102
$\bar{P}_{AW}$ (cmH_2O)	0.4±1.0	0.1±1.4	5.5±1.0*
pH	7.33±.06	7.34±.03	7.35±.04
PCO_2 (mmHg)	45±4	44±4	43±6
PO_2 (mmHg)	172±43	171±44	166±48
W_I (mJ/L)	532±160	690±231	171±65*
HR (/min)	63±8	64±8	64±9
MAP (mmHg)	83±18	81±19	79±15

* $p<0.001$ vs Circle and Demand

Discussion: We conclude that if preserving spontaneous breathing is desirable in patients who require general anesthesia, pressure support ventilation will decrease work of breathing significantly, with only a slight increase in airway pressure.

S42

Title: A NEW POSTANESTHETIC DISCHARGE SCORING SYSTEM FOR AMBULATORY SURGERY

Authors: F. Chung MD FRCPC., D. Ong MD., C. Seyone MD., N. Mati MD., P. Powell BA. RN., V. Chan MD FRCPC.

Affiliation: Toronto Western Division, The Toronto Hospital, University of Toronto, Toronto, Ontario

INTRODUCTION: The postanesthetic scoring system used in the recovery room immediately after anesthesia determines patient's recovery but does not evaluate home readiness of ambulatory surgery patients. Clinical discharge criteria (CDC) are usually used. No objective scoring system exists which systematically determines home readiness. In this study, a new Post-Anesthetic Discharge Score (PADS), which uses numerical values in assessing patient recovery and discharge readiness, is compared against the existing CDC.

METHODS: Following institutional approval and informed consent, 70 patients scheduled for an elective dilatation and curettage (D&C) were studied. A standard anesthetic regimen was used. All were seen by an investigator every 30 min. postop. commencing 1 h. after the operation up until discharge. At each postop. visit, all patients were scored using both the PADS and CDC. PADS consists of the following criteria.

1. Vital signs
2 = Within 20% of preop. value
1 = 20-40% of preop. value
0 = >40% preop. value

2. Activity and mental status
2 = Oriented x 3 *AND* has a steady gait
1 = Oriented x 3 *OR* has a steady gait
0 = Neither

3. Pain, nausea and/or vomiting
2 = Minimal
1 = Moderate, having required treatment
0 = Severe, requiring treatment

4. Surgical bleeding
2 = Minimal
1 = Moderate
0 = Severe

5. Intake and output
2 = Has had PO fluids *AND* voided
1 = Has had PO fluids *OR* voided
0 = Neither

The total score is 10 with patients scoring ≥8 being considered fit for discharge. The CDC used in our hospital are: *stable vital signs, alertness and orientation, absence of nausea and/or vomiting, a steady gait and no significant bleeding*. The time taken to obtain a PADS score ≥8 and to fulfill all CDC were recorded. These results were not made known to those directly involved in the care of the patients nor any influence exerted on the actual discharge time. The time that the patients were actually discharged from the ambulatory surgical unit were noted. All patients were contacted by telephone one day postop. Data was analyzed using absolute relative differences among variables. Results are expressed as Mean ± SD.

RESULTS: Patients required 108.6 ± 28.24 min. postop. to achieve a PADS score of ≥8 as compared to 124.5 ± 34.06 min. needed for a satisfactory CDC ($p<0.0001$). There was also a close correlation between the % of patients who could have been discharged using either PADS or the CDC at 2.5, 3.0 and 3.5 h. postop. At 1.5 h. postop., 62.8% of the patients could have been discharged using PADS versus only 28.6% by using the CDC ($p<0.0001$, Figure 1). The actual postop discharge time was 184.7 ± 48.1 min. which was significantly longer than the time needed to achieve either a PADS ≥8 or a satisfactory CDC. There were no post-discharge complications in any patient.

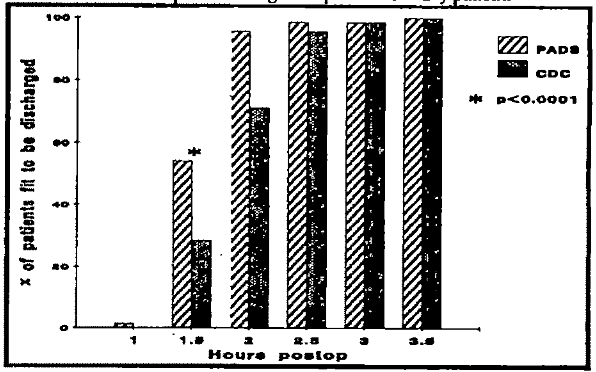


Figure 1

CONCLUSION: There is a close correlation between PADS and the CDC postop. from 2.0 h. onwards. More patients can possibly be discharged earlier by using PADS than the existing CDC as early as 1.5 h. postop. PADS can therefore potentially be a simple, time effective and objective assessment of all ambulatory surgery patients.

S43

Title: EFFECT OF INCREMENTAL PEEP ON PaO_2 AND SVO_2 DURING OLV

Authors: E. Cohen,M.D., O. Salter, M.D., J. Ali, R.N.
Affiliation: Anesthesiology Dept., Mount Sinai Medical Center, New York, NY 10029

The application of a single dose PEEP to the dependent lung during one lung ventilation (OLV) has shown to either decrease or have no effect on arterial oxygenation (PaO_2).[1,2] This study aimed to assess the effect of incremental PEEP (cm H2O) to the dependent lung (dose-response) on PaO_2 and mixed venous oxygen saturation (SVO_2).

Written informed consent was obtained from 11 ASA II-III patients scheduled for thoracic surgery. Anesthesia was induced with thiopental and maintained with enflurane, fentanyl, vecuronium and 100% O_2. Measurements were made at 15 minute intervals during baseline OLV , OLV+PEEP 5, OLV+PEEP 10, OLV+PEEP 15 , OLV+PEEP 20 , and return to OLV with no PEEP. Multiple comparison (ANOVA) and paired t-test were used for statistical analysis.

The Mean+SD values of all the stages are reported in the table. Statistical significance refers to comparison of each stage to baseline OLV. The application of incremental PEEP has minimal effect on PaO_2. No improvement or decline in PaO2 were observed even with the application of high PEEP. Although PEEP 5-15 did not influence PaO_2 or CO, the application of PEEP 20, substantially reduce SVO_2 due to a decrease in CO.

In conclusion, there are no indications that PEEP 5-20 are beneficial in improving PaO_2 during OLV and cannot be recommended for treating hypoxemia. Furthermore, high dose of PEEP (20) compromise CO and SVO_2 due to a reduction in oxygen delivery.

References
1. Anesth Analg 59: 847-851, 1980.
2. J Cardicthorac Anesth 2: 34-40, 1988

EFFECT OF INCREMENTAL PEEP

STAGES	OLV	PEEP 5	PEEP 10	PEEP 15	PEEP 20	OLV
PaO2 mmHg	147 ± 71	147 ± 87	160 ± 66	162 ± 68	111 ± 48	143 ± 67
CO L\min	4.7 ± 1	5.0 ± 1.2	4.6 ± 0.9	4.1 ± 1	✣ 3.8 ± 0.9	4.3 ± 1
SVO2 %	80 ± 5	78 ± 7	80 ± 6	75 ± 7 ✣	68 ± 8 ✳	76 ± 8

mean ± SD ✣ = $p < 0.05$ ✳ = $p < 0.001$

S44

TITLE: ST SEGMENT ANALYSIS DURING DELIBERATE HYPOTENSION

AUTHORS: S. Cohen, MD, D. Mathews, MD, and C. Weissman, MD
AFFILIATION: Departments of Anesthesiology and Medicine, Columbia University, New York NY 10032

Deliberate hypotension is often employed during orthopedic surgical procedures to decrease blood loss. Many patients having this type of surgery are elderly and therefore have an increased incidence of cardiovascular disease but symptoms may be masked preoperatively by their immobility. We examined changes in heart rate, blood pressure, and ST segments before, during, and after deliberate hypotension to determine whether hypotension was associated with perioperative myocardial ischemia.

The study, approved by the Institutional Review Board (consent not required), included 14 patients 27-87 years old (mean 62 ± 20 years). Nine patients were over 55 years old. There were 4 males and 10 females, thirteen of them had total hip replacement and one Harrington rod placement. Five were hypertensive (3 treated, 2 untreated). One had non-insulin dependent diabetes mellitus and one had a history of an MI 30 years preoperatively. Four patients were smokers and one was the recipient of a renal transplant. All patients had general anesthesia. Nine received narcotics, benzodiazepines, nitrous oxide, and isoflurane; in the remaining five patients, isoflurane was omitted. Twelve had hypotension induced with sodium nitroprusside, one with intravenous nitroglycerin, and one with both. Six patients also received beta-blockers and one received hydralazine. Blood pressure measurements were made using intra-arterial catheters.

Mean arterial blood pressure (MAP) and heart rate (HR) were as follows:

	Preop	Prehypo	Midhypo	RR Admit	RR Discharge
MAP	97.5±12	85.9±8 [1]	69.9±9 [2]	98.3± 16 [3]	93.3±10
HR	74.7±7	64.5±11 [1]	60.5±9	81.2±20 [3]	76.1±12

[1] Preop vs. Prehypotension (Prehypo) $p > 0.05$
[2] Prehypo vs Midhypotension (Midhypo) $p < 0.05$
[3] Midhypo vs RR Admit $p < 0.05$
Values are mean ± SD

ST segment analysis was performed with a Q-Med ST segment analyzer (Clark, NJ) beginning prior to induction of anesthesia and ending prior to discharge from the recovery room.

One patient had bigeminy on induction of anesthesia. ST segment depression of ≥1mm was seen in one patient (age 65) at the conclusion of anesthesia. ST segment elevation of ≥1mm was noted in one patient (age 31) on 9 different occasions. Two patients had inverted T waves not noted on preoperative ECG which disappeared on the first postoperative day. Neither patient had intraoperative ST segment changes and enzymes failed to confirm a myocardial infarction.

This study demonstrates a low (14%) incidence of ST segment changes consistent with myocardial ischemia despite significant reductions in blood pressure (28±10%) during deliberate hypotension. The incidence of ST segment changes was similar in patients older and younger than 55 years. This low incidence may be due to patient selection since deliberate hypotension is avoided in patients with coronary artery disease. This may also be due to prevention of tachycardia and the use of nitroprusside and nitroglycerin which decrease systemic vascular resistance (SVR). In contrast, untowards effects of hypovolemic hypotension may be related to increased SVR and tachycardia.

S45

Title: BACK PAIN THERAPIES: OBJECTIVE, REPRODUCIBLE OUTCOME DETERMINATION

Authors: M.L. Cohn, M.D., Ph.D., A.F. Machado, M. Cohn, CRNA
Affiliation: Surf Medical Center, Torrance, CA 90505

Since etiology of chronic low-back pain (CLBP) is unknown[1], treatment is empirical. It was reported that epidural morphine (preservative free-MO) and methylprednisolone acetate (MP) provides long-term pain relief to patients with postlaminectomy CLBP[2]. Other authors reported that epidural MO and MP failed to suppress CLBP[3,4]. Here, we used accurate, objective range of motion (ROM)[5] studies to verify therapeutic outcome.

Twenty adults with CLBP signed informed consent in accordance with institutional guidelines. Protocol included history, physical examination, CAT or MRI scan, noninvasive ROM[5], and Visual Analog Scale (VAS) scoring, fasting overnight, intravenous fluids, 24hrs monitoring respiration, ECG, blood pressure, and heart rate, two epidural catheters (inserted at L1-2 and caudally), and lumbar epidurogram. Iohexol was used to confirm proper placement of catheters and view epidural space. MO (4mg/4ml) was injected via upper catheter followed by flush of 8ml sterile normal saline (SNS). One hour later, via same catheter, MP (80mg/2ml) was injected followed by flush of 8ml SNS. Same sequence was repeated via caudal catheter; catheters were then withdrawn. Pruritus, nausea, vomiting, somnolence, and urinary retention were treated symptomatically. One month later, physical examination, ROM, and VAS were repeated. Epidurogram demonstrated partial occlusion in 17 patients and total occlusion in 3. Nonetheless, all patients experienced minor side effects; no patient experienced respiratory depression. At follow-up examination, VAS indicated significant pain relief in 16 patients. Those patients who reported improvement on VAS exhibited increased mobility. ROM improvement in individual patients did not always occur in all planes of motion, i.e., flexion, extension, lateral flexion, and axial rotation. One patient who failed to report pain relief had non-reproducible ROM both prior to and following therapy. The other three who reported no improvement had no change in ROM.

The present study attempted to avoid subjectivity of outcome determination by including objective ROM, validated in previous studies[5], as well as VAS scoring at all evaluations. Complexity of CLBP precludes possibility of obtaining well-matched groups of patients. Here, intra-individual comparisons ensured that each patient served as his/her own control. Evidence obtained with ROM objectively demonstrated functional improvement in all patients who reported decreased pain intensity on VAS. Interestingly, malingering is readily detectable by erratic fluctuations in ROM. All back pain therapies which claim to be efficacious can now be validated by accurate, noninvasive ROM.

References

1. Int. Disabil. Stud. 9(1):22-23,1987
2. Spine 11(9):960-963,1986
3. Anesthesiology 67(3):408-411,1987
4. Pain 36(3):297-303,1989
5. Arch. Phys. Med. Rehabil. 70:455-457,1989

S46

Title: MECHANISM OF THE POSITIVE INOTROPIC EFFECT OF KETAMINE HCl IN ISOLATED FERRET VENTRICULAR MYOCARDIUM

Authors: D.J. Cook, M.D. and P.R. Housmans, M.D., Ph.D.
Affiliation: Dept. Anesth. and Pharmacol., Mayo Foundation, Rochester, MN 55905

Ketamine stimulates the cardiovascular system through sympathomimetic effects. Yet its inotropic effect was reported as positive in rat (1) or negative in rabbit (2) ventricular myocardium. This study reexamines the effects of ketamine on the contractile properties of mammalian ventricular myocardium.

Methods. With approval of the IACUC, we assessed the concentration-dependent inotropic effect of ketamine HCl (10^{-6}M to 3×10^{-4}M in 0.5 log M increments) alone and in various pharmacologic conditions designed to delineate ketamine's site(s) of action in electrically stimulated ferret right ventricular papillary muscles (30°C, 0.25 Hz).

Results. Ketamine exerted a concentration-dependent positive inotropic effect that was maximal at 10^{-4}M. Bupranolol HCl (10^{-7}M) or pretreatment with reserpine abolished this positive inotropic effect while phentolamine HCl (10^{-6}M) did not. Simultaneous exposure to neuronal and extraneuronal norepinephrine uptake inhibitors desmethylimipramine HCl (DMI) 5×10^{-6}M and corticosterone 5×10^{-5}M also eliminated ketamine's positive inotropic effect. In the presence of corticosterone alone, ketamine's inotropic effect was smaller than that in corticosterone's absence. Ketamine produced a small increase in force in the presence of DMI, but this did not reach statistical significance.

Discussion. Ketamine exerts a positive inotropic effect mediated through activation of the β-adrenoceptor. Experiments with reserpinized muscles show this to be an indirect effect. Studies done in the presence of DMI and corticosterone indicate that ketamine's effect is to inhibit norepinephrine uptake at the neuroeffector junction rather than to augment norepinephrine release. Inhibition of neuronal catecholamine uptake is the dominant mechanism of action of ketamine's positive inotropic effect.

Support: NIH GM 36365 and Mayo Foundation.

References

1. Riou B, et al: Anesthesiology 71: 116, 1989.
2. Komai H, et al: Anesthesiology 71: A506, 1989.

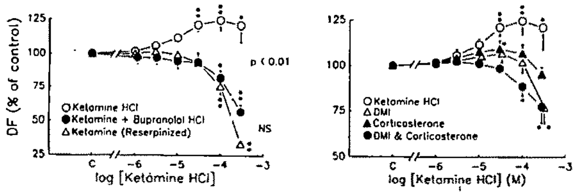


Figure 1. Left: Effect of ketamine HCl alone and in muscles pre-exposed to (±)-bupranolol HCl or reserpine. Right: Effect of norepinephrine uptake inhibitors on ketamine's inotropic effect.
$^*p < 0.05$, $^{**}p < 0.01$ for comparison with control. (Repeated measures analysis of variance followed by Dunnett's test when appropriate.)

S47

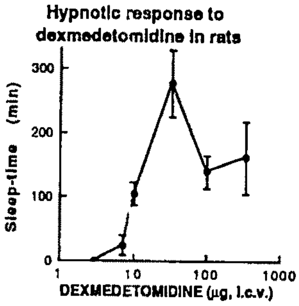
TITLE: DEXMEDETOMIDINE, AN α_2 ADRENERGIC AGONIST, EXERTS A BIPHASIC ANESTHETIC AND ANALGESIC RESPONSE IN THE RAT C.N.S.

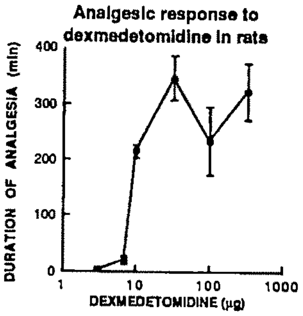
AUTHORS: C. Correa-Sales, M.D., T-Z. Guo, M.D., T.L. Yaksh, Ph.D., M. Maze, M.B.
AFFILIATION: Departments of Anesthesia, Stanford University, Palo Alto, CA 94304 and U.C.S.D., San Diego, CA & Anesthesiology Service, VAMC, Palo Alto, CA.

INTRODUCTION:The α_2 adrenergic agonists are a novel class of hypnotic-anesthetic agent with selectivity for specific binding sites through which these compounds exert their pharmacologic response[1]. This selectivity facilitates a systematic characterization of the molecular mechanism of anesthetic action including the sites of activity of α_2 agonists in the brain. As a step towards the characterization of its anesthetic site of action we now report on the dose-response characteristics of dexmedetomidine (dex), a highly-selective and potent α_2 adrenergic agonist, delivered directly into the central nervous system.

METHODS: Following institutional approval from Animal Care and Use Committee, rats had a stainless steel cannula inserted into the lateral ventricle under stereotaxic control and cemented firmly to bone screws. Four to 7 days later, a 30 g stainless steel needle was inserted through the cannula and positioned 1 mm beyond the tip of the cannula. Confirmation of the intraventricular site of injection was established by recovering methylene blue dye in the CSF at necropsy. Freshly prepared solutions of dex (1 to 300 µg) was injected over 30 s in a total volume of 10 µl and the sleep-time (duration of loss of righting reflex) and duration of maximal analgesic effect (by the tail flick latency response) were assessed. Data were analyzed by ANOVA and t test where appropriate.

RESULTS: Data are presented from 40 rats in which correct placement of the cannula was verified. Loss of righting reflex was noted at 5µg and its duration was proportional to dex dosage, up to 30 µg (Fig. 1) Beyond this dose there was a decrease in sleep-time with dose. Prolongation of the tail flick latency response was noted at 3µg and reached the maximum cutoff of 20 sec by 5µg. Thereafter the duration of maximal analgesia was proportional to dose up to 30 µg (Fig 2). Again, this response was biphasic. Deaths occurred consistently at doses ≥ 1000 µg.





DISCUSSION & CONCLUSIONS:These studies demonstrate the extreme range of efficacy, and safety present with dex, as well as the biphasic nature of the anesthetic and analgesic responses to dexmedetomidine. Administration of dex in the linear portion of the dose-responce curve should allow us to establish the intracerebral sites for the anesthetic action of the α_2 agonists.

REFERENCE:Anesthesiology 71:75-79, 1989

ACKNOWLEDGEMENTS:NIH(GM30232),VA,&,FarmosRes. Group.

S48

TITLE: INTRACORONARY ISOFLURANE CAUSES MARKED VASODILATION IN CANINE HEARTS

AUTHORS: GJ Crystal, PhD, S-J Kim, MS, EA Czinn, MD, MR Salem, MD, WR Mason, MD
AFFILIATION:Depts of Anes, IL Masonic Med Ctr and Univ IL Coll Med, Chicago, Il 60657

Previous studies of coronary vasomotor effects of isoflurane were complicated by changing systemic hemodynamic conditions and global cardiac work demands (1). Accordingly, present study was performed in which extracorporeal perfusion system was used to introduce isoflurane selectively into left anterior descending coronary artery (LAD) of in situ canine hearts.

The protocol was approved by our Institutional Animal Investigation Committee. Seven mongrel dogs were anesthetized with fentanyl and pentobarbital, intubated and mechanically ventilated, and left thoracotomized. In each dog, the LAD was cannulated and perfused with isoflurane-free blood (Control) and with blood equilibrated in extracorporeal oxygenator with isoflurane (0.5, 1.0, and 2.0 % in 95.5 % O_2 - 4.5 % CO_2). The order of the isoflurane concentrations was randomized. LAD perfusion pressure was maintained at 100 mmHg. Coronary blood flow (CBF; in $ml \cdot min^{-1} \cdot 100g^{-1}$) was measured electromagnetically. Radioactive microspheres were used to assess endocardial:epicardial distribution of flow (En/Ep). Local venous blood was analyzed for PO_2 and O_2 content. Fick equation was used to calculate myocardial O_2 consumption (MVO_2; in $ml \cdot min^{-1} \cdot 100g^{-1}$). Steady state responses during isoflurane were compared to those during maximal vasodilation with adenosine. Statistical analysis was performed with ANOVA and Student-Newman-Keuls test.

Intracoronary isoflurane caused significant dose-dependent increases in CBF that were transmurally uniform (Table 1). The accompanying increases in venous PO_2 and increases in AVO_2 were disproportionate to isoflurane-induced flow increases reflecting reduced MVO_2. With 2.0 % isoflurane, increase in CBF was 80 % of the adenosine-induced maximal response.

The present study demonstrates that isoflurane causes dose-dependent coronary vasodilation via a direct relaxatory effect on vascular smooth muscle. The potency of this effect is evidenced by isoflurane-induced increases in coronary blood flow that were nearly equal to those achieved during maximal dilation with adenosine.

Reference

1. Still JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C: Anesthesiology 66:273-279, 1987

Table 1. Effects of isoflurane and adenosine.

	CONTROL	ISOFLURANE			ADENOSINE
		0.5%	1.0%	2.0%	
CBF	92±4	230±33*	269±37*	446±48*	550±79*
MVO_2	8.1±0.4	5.1±1.3*	5.4±1.0*	4.3±1.1*	8.1±1.3
AVO_2	8.8±0.4	2.7±1.0*	2.3±0.5*	1.1±0.4*	1.6±0.3*
PvO_2	32±1	70±8*	83±9*	130±21*	71±7*
En/Ep	1.3±0.1	-	1.3±0.2	1.0±0.1	1.3±0.1

Results are Mean±SE. * P<0.05, from CONTROL.

Supported in part by AHA of Metropolitan Chicago.

S49

TITLE: PROPOFOL MARKEDLY INHIBITS SYMPATHETIC ACTIVITY: ASSESSMENT OF NE KINETICS IN DOGS

AUTHORS: R Deegan, MD, HB He, Pharm D, AJJ Wood, MD, M Wood, MD

AFFILIATION: Departments of Anesthesiology and Pharmacology, Vanderbilt University, Nashville, TN 37232.

INTRODUCTION: In common with many anesthetic agents, propofol is a cardiovascular depressant. This may be at least partly due to sympathetic inhibition (1). Changes in plasma norepinephrine (NE) concentrations are a poor index of in vivo sympathetic activity because they depend on NE plasma clearance (CL) as well as NE release from sympathetic nerve endings. NE release can be assessed by determining NE spillover into plasma. The aim of this study was to define, using isotope dilution techniques (2), the effects of propofol anesthesia on NE concentration, NE-CL and NE spillover (SO) in dogs.

METHODS: A trace dose of ^{3}H-NE was infused IV and plasma ^{3}H-NE (dpm/ml) and unlabeled endogenous NE (pg/ml) were determined at steady state. NE-CL and NE-SO were calculated:

$$SO = \frac{^3\text{H-NE infusion rate (dpm/min)}}{\text{specific activity of plasma NE (dpm/pg)}}$$

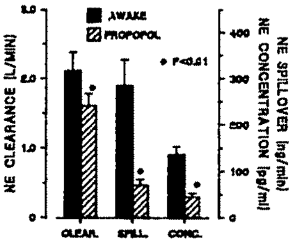
$$CL = \frac{^3\text{H-NE infusion rate (dpm/min)}}{\text{plasma } ^3\text{H-NE concentration (dpm/ml)}}$$

With institutional approval, 8 female dogs (mean wt=23.2kg) trained to lie quietly, were studied awake and during propofol anesthesia (6 mg/kg induction and 0.8 mg/kg/min for maintenance). 15μCi of ^{3}H-NE (in 0.9% saline with 1 mg/ml ascorbic acid) was infused IV over 1 min followed by 0.6 μCi/min for 50 mins. Arterial blood samples for measurement of ^{3}H-NE and NE were taken prior to, and at 20, 30, 40 and 50 mins during the infusion. NE was measured by HPLC with electrochemical detection and ^{3}H-NE by liquid scintillation counting of the HPLC eluent coinciding with the NE peak. Statistical analysis was by Student's paired t-test.

RESULTS: Propofol reduced plasma NE concn by 65% (p<0.001) (Fig). This was due to a profound decrease in NE SO of 73% (p=0.005) There was a small effect on NE-CL (22% reduction, p<0.01).

DISCUSSION: The reduction in NE spillover by propofol indicates a marked inhibition of NE release from sympathetic nerve endings. In the absence of a large decrease in NE-CL (which would tend to increase plasma NE), the decreased NE spillover resulted in a corresponding marked decrease in plasma NE concn during propofol anesthesia. These findings with the IV anesthetic propofol can be compared with our previous work with the inhalational anesthetic, halothane (3). When halothane (2.0MAC) produced a similar (72%) reduction in spillover to that produced by propofol (73%), halothane resulted in a 45% reduction in CL in contrast to only 22% with propofol.

EFFECT OF PROPOFOL ON NE KINETICS



REFERENCES: 1) Anesthesiology 69: A639, 1988. 2) J Cardiovasc Pharmacol 4: S152-7, 1982. 3) Anesthesiology 1990 (in press).

S50

THE EFFECT OF ENFLURANE (1 MAC) ON THE NORMAL AV CONDUCTION SYSTEM AND ACCESSORY PATHWAYS

WB Dobkowski FRCPS, JM Murkin FRCPS, MD Sharpe FRCPS, N Molotiu MD, G Guiraudon FRCPS, R Yee FRCPS. Departments of Anaesthesia, Cardiology and Cardiovascular Surgery, University Hospital, University of Western Ontario, London, Ontario, Canada.

Introduction: Many investigations, mainly carried out in animals, have shown a depressive effect of inhalational anaesthetics on the atrioventricular (AV) conduction system.[1] The effect of Isoflurane and Halothane on the normal AV conduction and accessory pathways (AP) in patients with Wolff-Parkinson-White (WPW) Syndrome, was studied in our institution and reported.[2,3] These studies show that both Isoflurane and Halothane depressed the normal AV and AP conduction. Because the effect of Enflurane on AP conduction has not been reported, we investigated the influence of this anaesthetic on electrophysiologic (EP) properties of the normal AV and AP conduction in a similar group of patients with WPW Syndrome during cryoablation of the AP.

Methods: Following approval from the Ethics Committee, seven patients, two women and five men aged 19-34, were investigated. Patients had premedication with Lorazepam 0.06mg/kg PO and Morphine 0.1mg/kg IM. Anaesthesia was induced with Sufentanil 20μg/kg and Vecuronium 20μg. Monitoring included: an arterial line, CVP catheter, pulse oxymeter, end-tidal capnography (E_tCO_2) and temperature. The depth of anaesthesia was monitored with Monitor 222 Puritan Bennett. After sternotomy, a baseline EP study using epicardial hexapolar electrodes measured: 1) Right atrial refractory period (RARP) at cycle length 500msec and 400msec (including atrial effective refractory period (AERP), atrioventricular effective refractory period (AVERP) and accessory pathway (APERP). 2) Right ventricular effective refractory period (RVERP) at cycle length 400msec and retrograde accessory pathway refractory period (APERP) and 3) shortest cycle length with 1:1 conduction (SCL). Enflurane was then administered to the level of 1.68 E_t Volume % and stimulation was repeated. Paired T-test (p<0.05) for significance was used to analyze data.

Results: Following the administration of Enflurane we observed significant (p<0.05) prolongation of conduction within: accessory pathway (SCL-AP), (APERP) and significant (p<0.05) increase of RAERP and AVERP. Also statistically significant (p<0.05) depression of the normal AV system in antegrade and retrograde conduction existed. RVERP was prolonged. (see Table #1)

Discussion: Enflurane depressed conduction in normal AV system and accessory pathway. Therefore we could suggest that: 1)Enflurane may alter or increase incidence of arrythmias in WPW patients undergoing noncardiac or cardiac surgery. 2)May change in mapping (potentially conceal the pathway) during accessory pathway cryoablation. 3)Enflurane should not be used as an anaesthetic for WPW patients. 4)Compared with Isoflurane and Halothane[2,3] Enflurane seems to be the strongest depressant of AV and AP conduction.

References:
1) Atlee J.L. et al., Anesthesiology 1989:71:941-952.
2) Dobkowski W.B. et al, Anesthesia & Analgesia 1990:70:2S, S86.
3) Sharpe M.D. et al, Anesthesia & Analgesia 1990:70:2S, S356.

THE EFFECT OF ENFLURANE (1MAC) ON THE NORMAL A-V CONDUCTION SYSTEM AND ACCESSORY PATHWAYS

* P<.05

ANTEGRADE CONDUCTION	CONTROL (msec)	ENFLURANE (msec)
SCL-AP	289 ± 27	388 ± 19 *
SCL-AV	278 ± 44	325 ± 44 *
RAERP	180 ± 24	273 ± 25 *
AVERP	222 ± 29	352 ± 55 *
APERP	317 ± 24	434 ± 49 *
RETROGRADE CONDUCTION	**CONTROL (msec)**	**ENFLURANE (msec)**
SCL-VA	212 ± 19	240 ± 18 *
RVERP	189 ± 21	212 ± 21

S51

Title: **Subjective Effects of Nitrous Oxide in Normal Volunteers**

Authors: C.S. Dohrn, M.A., J.P. Zacny, Ph.D., J.L. Lichtor, M.D., R.S. Finn, M.D., D.W. Coalson, M.D., H. deWit, Ph.D.
Affiliation: Departments of Anesthesia and Critical Care and Psychiatry, University of Chicago, IL

Introduction: Nitrous oxide (N_2O), commonly used as an anesthetic, is also used recreationally. Acute abuse has led to harm (e.g., from falling down) and even death.[1] These adverse effects have led some to believe that nitrous oxide should be as closely regulated as are other drugs with high abuse potential.[2] The purpose of the present study was to examine the abuse potential of N_2O, specifically the mood-altering effects of a range of concentrations of N_2O, using assessment techniques that have been developed and refined by human behavioral pharmacologists.[3]

Methods: After approval from the Clinical Investigations Committee and informed consents were obtained, five men and two non-pregnant women (mean age, 24.1) participated in a randomized, placebo-controlled, crossover trial during five experimental sessions at 3-day intervals. After subjects were seated comfortably and fitted with a clear face mask, they breathed compressed air for a baseline period of ten minutes. They were then told they would breathe either drug or placebo for the next 30 minutes. They inhaled one of two "placebo gases," i.e., compressed air or 100% oxygen, or one of three concentrations of N_2O (10%, 20%, or 40%) in oxygen. An anesthesiologist administered the agents; the experimenter and the subject were blind to agents inhaled. After the inhalation period, subjects remained in the laboratory for one hour of recovery. During baseline, inhalation, and recovery periods, subjects completed two standardized mood questionnaires, the Profile of Mood States (POMS) and the Addiction Research Center Inventory (ARCI), as well as a Visual Analogue Scale (VAS), an auditory reaction time test, and the Digit-Symbol Substitution Test (DSST). Repeated measures analysis of variance was used to analyze N_2O effects with $p \leq 0.05$ considered significant.

Results: Oxygen, air, 10%, and 20% N_2O had little or no effect on mood or psychomotor performance. Scores of those who inhaled 40% N_2O significantly increased on the following scales of the ARCI: the MBG (a general measure of drug-induced euphoria), LSD (a measure of dysphoria and somatic symptoms), and M (a measure of marijuana-like effects) and on the Stimulated and High scales of the VAS. These mood effects generally dissipated by 30 min. after discontinuing N_2O. After 40% N_2O, scores from the Anxiety scale of the POMS increased significantly during the recovery period. Performance on the DSST was significantly impaired only during the inhalation period of 40% N_2O. N_2O did not affect ART.

Discussion: Nitrous oxide appears to have some subjective effects that are similar to those of other drugs that are highly abused (e.g., marijuana, cocaine).[4] Since N_2O has euphorigenic subjective effects, it, like other drugs of abuse (e.g., fentanyl), should be more closely regulated in the medical setting.

References:

1. New York Times, sec.B, 1, P.B2, Feb. 20, 1979.
2. JAMA, 255: 1913-1920, 1986.
3. Psychopharmacology, 81:144-149, 1983.
4. J Pharm Exp Ther, 242:777-783, 1987.

S52

TITLE: **CONTROLLED HYPOTENSION BY PROSTAGLANDIN E1 IN NORMOTENSIVE AND HYPERTENSIVE PATIENTS**

AUTHORS: S.Dozaki,M.D., A.Okamura,M.D., Y.Morimoto,M.D., Y.Komura,M.D., S.Kaseno,M.D., O.Kemmotsu,M.D.
AFFILIATION: Dept. Anesth., Hokkaido Univ. Sch. of Med.,Sapporo 060,Japan

Prostaglandin E1 (PGE1) seems to be useful in controlled hypotension since it maintains cerebral, renal and coronary blood flows even at the low levels of arterial blood pressure. We evaluated the efficacy of PGE1 as a hypotensive agent for controlled hypotension in both normotensive and hypertensive patients, and compared effects of PGE1 on hemodynamics between two groups.

One hundred seventy seven patients who had indications of controlled hypotension were studied after institutional approval and informed consent. They were divided into two groups:138 normotensive (group A) and 39 hypertensive patients (group B). Anesthesia was induced with thiamylal and the trachea was intubated with vecuronium. Anesthesia was maintained with enflurane in nitrous oxide and oxygen. The initial systolic blood pressure was reduced to 80-90 mmHg in group A and to 2/3 of the control value in group B with an infusion of 0.1-0.2ug/kg/min PGE1, and maintained with an infusion of 0.05-0.1 ug/kg/min PGE1. Operating time, anesthesia time, onset time and recovery time of PGE1 induced hypotension and urine output were measured. Cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) and urine index (urine output/(infusion + transfusion volume - blood loss)) were also evaluated pre-, during, and post-hypotension.

There were no differences in onset time, recovery time, CI and PCWP between groups. CI during PGE1 infusion in both groups increased significantly and CI of 30 min after PGE1 in group B showed 130% of the control. Although urine index of group A did not change, that of group B increased significantly 30 min after PGE1 administration.

Our results suggest that controlled hypotension by PGE1 infusion is suitable in hypertensive patients whose organ blood flows should not be decreased during hypotension, because both CI and urine index were increased during hypotension induced by PGE1. PGE1 seems to improve cardiac function with reduction of afterload, which is also feasible in hypertensive patients. In conclusion, our results indicate that controlled hypotension by PGE1 infusion can be safely applied to hypertensive patients as well as normotensive patients.

S53

TITLE: ANALYSIS OF RENAL FUNCTION DURING CONTROLLED HYPOTENSION WITH PGE$_1$, TNG OR TMP IN HUMANS

AUTHORS: S. Dozaki, Ph. D. *, A. Okamura, M. D., T. Yamamura, Ph. D., O. Kemmotsu, Ph. D.
AFFILIATION: Dept. of Anes., Hokkaido Univ. Sch. of Med., JAPAN.
* Oregon Health Sciences University, OR 97201.

Controlled hypotensive anesthesia has been applied to reduce blood loss, to keep the operating fields dry, and for subsequent decreasing the chance and volume of transfusion. But, from the point of organ perfusion and function controlled hypotension is not without risks. Decrease of urine volume has usually been experienced in controlled hypotension and it has been thought to represent a negative influence on renal function. In this study, α_1-microglobulin (α_1-M), β_2-microglobulin (β_2-M), N-acetyl-β-glucosaminidase(NAG) and creatinine clearance(Ccr) were measured as the indices of renal function during administration of either prostaglandin E$_1$ (PGE$_1$)[1, 2], trinitroglycerin(TNG) or trimethaphan(TMP), and compared with each other.

Twenty six ASA I and II patients who had indications for controlled hypotension for non-abdominal surgery were studied after institutional approval and informed consent. All cases had normal preoperative renal function assesssed by s-creatinine. They were divided into 3 groups: 14 for PGE$_1$, 5 for TNG and 7 for TMP. Premedication consisted of oral diazepam 10mg and ranitidine 150mg 2 hr before anesthesia. Anesthesia was induced with thiamylal 5mg/kg iv and the trachea was intubated after relaxation with vecuronium 0.1mg/kg iv. Anesthesia was maintained with 1.5-2% enflurane in 67% nitrous oxide and 33% oxygen. Hypotensive drugs were administered to reduce the systolic blood pressure to 80-90mmHg. Plasma and urine α_1-M, β_2-M, NAG and Ccr were measured before, during(30 min, 60 min) and after(30 min, 60 min) administration of each drug. All variables were expressed as mean±SEM, and statistical analysis was performed by ANOVA. P value of<0.05 was considered statistically significant.

There were no differences in age, body weight, operating time, anesthesia time, blood loss, urine volume, infusion volume and transfusion volume between groups. There were no significant differences in plasma and urine α_1-M and β_2-M. Ccr at 30 min during TNG administration was significantly decreased compared with PGE$_1$ and TMP(Table). At 60 min during and at 30 min and 60 min after TMP administration, NAG was increased(Table).

There are many methods used to evaluate renal function. β_2-M, NAG and α_1-M measurements were produced as quick response methods. Although all three methods seem to reflect both glomerular and tubular functions, α_1-M has been thought to have the highest specificity. In this study, TNG was associated with a decrease in Ccr during hypotension, while TMP patients showed increased NAG values after infusion. This indicates that PGE$_1$ may be a better choice for controlled hypotension with regard to renal function than TNG or TMP. It may also be suggested that NAG and Ccr are more useful than α_1-M and β_2-M for evaluation of renal function.

References
1. Anaesthesia 37:530-535, 1982
2. Acta Physiol. Scand. 75:161-169, 1969

Table Urine NAG and Ccr in PGE$_1$, TNG and TMP

	Urine NAG(U/L)			Ccr(ml/min)		
	PGE$_1$	TNG	TMP	PGE$_1$	TNG	TMP
Pre	4.40±0.87	4.45±1.15	5.34±1.65	148±19	143±31	157±49
D30	4.65±0.66	4.23±2.10	4.24±2.58	104±15	43±17*	107±18
60	5.33±1.22	4.87±2.35	8.17±3.39	102± 9	78±29	113±27
P30	6.12±1.16	7.08±2.63	15.40±4.54	101±24	111±24	128±14
60	5.50±0.85	5.73±1.75	11.25±2.23	115±35	97±23	72±17

*:$p<0.05$ vs PGE$_1$ and TMP (mean±SEM)

S54

Abstract Withdrawn

S55

Title: PREOPERATIVE PSEUDOCHOLINESTERASE LEVEL AS AN INDICATOR OF INTRAOPERATIVE BLOOD USAGE IN PATIENTS UNDERGOING ORTHOTOPIC LIVER TRANSPLANTATION

Authors: DA Dubbink, M.D., SR Rettke, M.D., R Sittipong, M.D., RAF Krom, M.D.
Affiliation: Mayo Clinic, Rochester, MN

Introduction: Pseudocholinesterase (Pche) levels have been found to be below normal in patients with severe liver dysfunction[1,2]. This enzyme's activity is reported to be a useful measure of liver function in patients with cirrhosis undergoing portocaval surgery[3]. We have retrospectively analyzed results from 179 consecutive patients undergoing first-time orthotopic liver transplantation (OLT) to assess the correlation between preoperative Pche levels and intraoperative blood requirements.

Methods: The anesthetic plan was isoflurane, fentanyl, lorazepam, and pancuronium. Pche levels were determined using the DuPont automatic clinical analyzer (normal values between 8-18 international units per ml). The patients were divided into two groups: Group A had Pche levels <8 IU/ml and group B had levels $\geq$8 IU/ml. Total blood transfusions were compared in the two groups using a two-tail T-test. P values less than 0.05 were considered significant. All results are reported as the mean ± SEM.

Results: Patients in group A required a mean of 24.36 ± 1.94 units of blood, whereas group B patients were transfused with a mean of 12.5 ± 1.54 units (Fig. 1; $P < 0.05$).

Discussion: Because Pche is synthesized by the liver, we suspected that decreased plasma levels would correlate with more severe hepatic injury and consequently these patients would require a larger volume of blood transfusion intraoperatively. Mechanisms likely responsible for this relation would include decreased levels of clotting factors, thrombocytopenia, and platelet dysfunction. A thorough preoperative anesthetic exam and laboratory evaluation remain important in assessing intraoperative anesthesia requirements. A useful part of this assessment appears to be a Pche level.

References: 1. Transplantation 23:404-6, 1977. 2. Lancet 2:1040-4, 1971. 3. Gut 1:303-11, 1960.

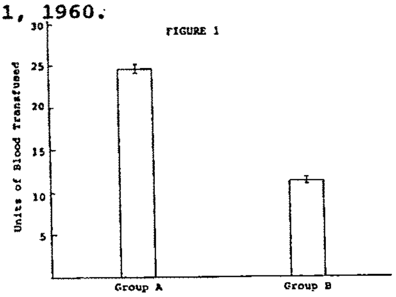


FIGURE 1

S56

Title: CALCIUM CHLORIDE REQUIREMENTS VERSUS FRESH FROZEN PLASMA TRANSFUSED DURING ORTHOTOPIC LIVER TRANSPLANTATION

Authors: DA Dubbink, M.D., SR Rettke, M.D., KA Williamson, M.D., R Sittipong, M.D., RAF Krom, M.D.
Affiliation: Mayo Clinic, Rochester, MN

Introduction: Ionized calcium levels are known to decrease during orthotopic liver transplantation (OLT)[1,2]. Transfusion of citrate containing blood products can produce ionic hypocalcemia requiring calcium chloride administration to restore adequate levels.

Methods: We reviewed the records of 179 consecutive patients undergoing initial OLT. The amount of fresh frozen plasma (FFP) transfused was compared to the total amount of calcium chloride ($CaCl_2$) administered. Ionized calcium was measured per protocol (Radiometer, Copenhagen, Denmark), and $CaCl_2$ was given to raise plasma levels toward the normal range (4.75-5.2 mg/dl). The linear regression method was used, and all results are expressed as mean ± SEM.

Results: There was a significant correlation between the amount of FFP transfused and the amount of $CaCl_2$ given ($R = 0.87$, $P < 0.05$) as shown in Figure 1.

Discussion: FFP is the fraction of whole blood which contains the largest amount of citrate[3]. Patients undergoing OLT have a decreased ability to metabolize citrate leaving them vulnerable to citrate-induced hypocalcemia. This data suggests that the amount of FFP used is most likely a cause of intraoperative ionic hypocalcemia.

References:
1. Transplantation 41:335-9, 1986.
2. Eur J Anes 4:421-7, 1987.
3. World J Surg 11:2-13, 1987.

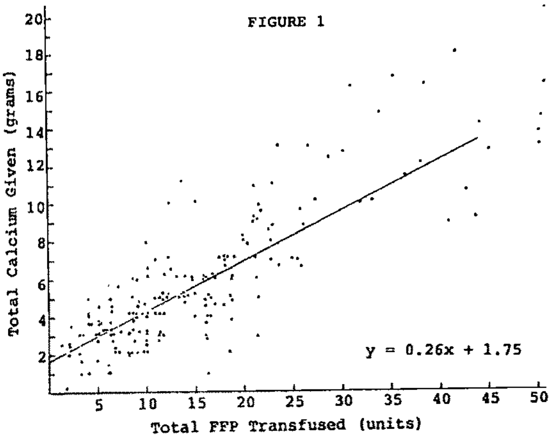


FIGURE 1

S57

TITLE: NEUROMUSCULAR EFFECTS OF ORG-9426 IN HUMANS DURING GENERAL ANESTHESIA WITH AND WITHOUT ENFLURANE

AUTHORS: M. Dubois, MD; B. Kataria, MD; D. Lea, RN, BSN; G. Lapeyre, MD

AFFILIATION: Georgetown University Medical Center, Washington, DC 20007

ORG-9426, a non-depolarizing steroidal muscle relaxant, has an onset time twice as fast as vecuronium in cats[1] and its ED95 in humans appears to be 285 mcg/kg[2]. Institutional approval was obtained and twenty ASA 1 or 2 consenting surgical patients, aged 18-65 years, were randomly assigned to one of two groups. After premedication and a thiopental induction, Group A utilized a balanced anesthetic technique with a narcotic maintenance (fentanyl up to 10 mcg/kg) with N_2O/O_2 and Group B utilized an anesthetic technique with enflurane maintenance (end tidal 0.5%) with N_2/O_2. The ulnar nerve was stimulated with supramaximal 2HZ Train-of Four (TOF) every 10 sec. Contractions of the thumb were quantitated with a force transducer and recorded. Endotracheal intubation was accomplished within 90 sec. following ORG-9426 injection of 600mcg/kg and scored accordingly. Maintenance doses of ORG-9426 were administered at a T_1 twitch recovery of 25%. At the end of the surgical procedure, all patients were reversed with neostigmine and glycopyrrolate. Measured parameters included: time intervals from injections of ORG-9426 to: 90% depression of T_1 (T_1 90% block); maximum T_1 depression (onset time); clinical duration (time for T_1 to reach 25% of control) for initial and subsequent maintenance doses; heart rate; blood pressure; and any adverse clinical experiences. Student's T-test was utilized for the data comparison between the two groups.

In both groups, ORG-9426 provided a rapid onset of blockade with an overall mean 96.7 sec. in order to reach T_1 90% block. Clinical duration of the initial (intubation) dose was longer in group B. Clinical durations of maintenance doses were significantly different between the 2 groups (Table 1). There were no signs of drug accumulation. In a limited number of patients, spontaneous recovery rates (25% to 75% T_1) were between 11 and 25 min. Pharmacological reversal was rapid and comparable to vecuronium. No clinically significant changes in heart rates or blood pressures were noted, nor were adverse clinical experiences noted. The particularly rapid initial development of neuromuscular blockade after ORG-9426 (600 mcg/kg) consistently allowed endotracheal intubation. Its predictable maintenance rate and its fast recovery in both balanced and inhalational anesthetic techniques fully warrant further clinical testing.

References:

1. British Journal of Anaesthesiology, 63, 400-10, 1989.
2. Anesthesiology, 71, A773, 1989.

TABLE I

	Group A Fentanyl (n=10)	Group B Enflurane (n=10)	TOTAL (n=20)
Intubation Dose (600 mcg/kg)			
T_1 90% Depression (sec.)	81.5 ± 10.1	111.9 ± 13.1	96.7 ± 8.8
Onset Time (sec.)	149.2 ± 20.7	185.5 ± 18.1	167.3 ± 14.0
Clinical Duration (min.)	29.4 ± 2.9	35.0 ± 2.8	32.2 ± 2.1
Maintenance Doses (150 mcg/kg)			
Duration (min.)	16.5 ± 0.9 *	22.6 ± 1.4 *	18.3 ± 0.87

Values are Mean ± SEM

* Statistically different $p \le 0.001$

S58

TITLE: ICU READMISSIONS: DO THEY REFLECT PREMATURE DISCHARGE?

AUTHORS: C. G. Durbin, Jr., M.D., R. F. Kopel, M.D., M. A. Orsina, M.B.A.

AFFILIATION: University of Virginia Health Sciences Center, Charlottesville, VA 22908

In times of limited critical care resources, and increasing demands for service, patients are spending fewer days in ICUs. Concern was raised that premature discharge may adversely affect outcome. With institutional approval, we examined in detail medical records of all patients who were readmitted to an intensive care unit after discharge during a one year period.

All patients readmitted to either the surgical or medical intensive care units (24 beds total) were identified by computer printout. Controls were matched by unit, sex, age and principal diagnosis when possible. Condition, vital signs, laboratory data, APACHE II score, and details of the post-discharge course were recorded. These factors were compared in the two groups.

There were a total of 1803 patients admitted to both units during this study. 83 patients were readmitted (4.6%) of which 53 patients died (64%). Mortality in the control group was 7%. Of patients readmitted, 26% presented with exacerbation of their original problem. The remaining patients developed a new problem which was respiratory in origin in 59%, cardiac in 18%, septic/infective in 18%, and renal failure in 5%. Initial APACHE II scores were higher on average in the readmission group versus the control patients (10.7 vs. 8.6).

Patients readmitted to an ICU experience very high mortality. Unlike previous reports, most of the readmissions were due to new problems developing after the first discharge[1,2]. On the average, patients readmitted were more ill as judged by initial APACHE II scores. About one quarter of patients readmitted may have been discharged prematurely as they were readmitted for worsening of their original ICU admission problem.

1. Discharge decision-making in a medical ICU: characteristics of unexpected readmissions. Crit Care Med 1983;11:61.
2. ICU readmission of surgical patients. Crit Care Med 1988;16:414.

S59

TITLE: SHOULD CPR BE WITHHELD FROM THE CHRONICALLY ILL AND ELDERLY?

AUTHORS: C. G. Durbin, Jr., MD, W. Smith, MD, M Orsina, MBA
AFFILIATION: University of Virginia Health Sciences Center,
Charlottesville, Virginia

Well-demonstrated to improve quality and quantity of life in the community setting[1], CPR has been less helpful in hospitalized patients[2]. Attempting to identify patients who will not benefit from CPR, the survival in several groups of patients has been found to be so poor as to contraindicate the use of CPR. Specifically, age greater than 70 and the presence of significant chronic disease or malignancy have been cited as factors which should mandate the withholding of CPR[3]. In an effort to examine the above suggestions in our own hospital, we reviewed the diagnoses and final outcome of all patients on whom CPR was performed during a recent 2 year period.

As a 750 bed acute care teaching institution, resuscitation efforts are provided by a designated team of (Advanced Cardiac Life Support certified) residents, nurses, and support personnel availible 24 hours a day within 5 minutes. Each time the cardiac arrest team is called a detailed clinical record form is completed by hospital policy and a copy returned to the hospital Resuscitation Committee for review.

With approval, medical records were reviewed on all patients sustaining resuscitative efforts. Patients were classified into disease categories using diagnosis coding and the medical record. The following categories were used: Multiple Medical Problems (MMP), 2 or more systems involved, usually physically debilitated; Malignancy (NEO) with or without metastases; Acute Events (AE), no pre-existing medical problems; Procedural Related (Proc), surgery, interventional radiography, cardiac catheterization; Congestive Heart Failure (CHF), all with this diagnosis who were not physically disabled; Trauma (TRA); Congenital (CONG), pediatric patients with known lesions; Burns (BURN); and AIDS. Each patient was classified into only one category, survival was to hospital discharge, outcome differences were tested by chi-square. Age greater than 70 was evaluated separately.

Results: 550 patients were studied. Initial survival, 62% (342) from the arrest was not different among the groups (chi sq = 18.8 10df $p < 0.1$). Over-all survival to discharge was 23% (126) and showed significant differences among groups (chi-sq = 22.44 10 df $p < .05$). Survival is shown in the following table. Survival in patients over 70 was 22%. P values indicate differences from the average.

Category	Alive/Total	% Survival	p-value
MMP	48/210	25%	< .001
NEO	7/53	13%	< .05
AE	22/85	26%	< .05
PROC	16/45	26%	< .05
CHF	19/46	29%	< .01
TRA	2/18	11%	n.s.
CONG	21/42	50%	< .001
BURN	3/13	23%	n.s.
AIDS	0/3	0%	n.s.
> 70 years	30/137	22%	n.s.

Unlike previous reports we found significantly good survival in debilitated patients with multiple medical problems and in patients over 70 years of age. The poor outcome in Trauma patients (11%) is consistent with other reports.

This study probably underestimates the actual use of CPR and survival in that brief (i.e. defibrillation in the CCU) episodes are not reported in the data base. The high survival rate demonstrated in most groups in this study probably reflects prior decisions to withhold CRP in many patients in whom it would have been ineffective. Use of CPR in this study of hospitalized patients is associated with significant survival and the decision to withhold it should be made in individual patients rather than by diagnostic classification.

References:
1. Mod Concepts Cardiovasc Dis 49:31-6, 1980
2. N Engl J Med 309:569,1983
3. JAMA 260(14):2069,1988

S60

TITLE; CAN UNCONSCIOUS LEARNING OCCUR DURING ISOFLURANE ANESTHESIA?

AUTHORS; R Dwyer FFARCSI, HL Bennett PhD, N Peterson BS, EI Eger II MD
AFFILIATION; University of California, San Francisco, California.

INTRODUCTION; Patients can retain information presented to them during anesthesia despite lack of conscious recall [1,2,3]. We studied whether learning occurred during anesthesia at different end-tidal concentrations of isoflurane (F_E').

METHODS; With approval of our Committee on Human Research we studied 24 healthy informed subjects aged 20-60 yr (mean 40±9) undergoing elective surgery. On the day before surgery, subjects were asked 15 curious questions whose answers were not likely to be known by the subjects e.g. what is the blood pressure of an octopus?. Anesthesia was induced by inhalation of isoflurane in nitrous oxide and oxygen (in 10 cases supplemented by propofol) and endotracheal intubation facilitated by vecuronium 0.1mg/kg. Anesthesia was maintained by isoflurane (with nitrous oxide eliminated by flows of 5l/min) at F_E' of 0.6 MAC; after 10 min, subjects received a taped message via headphones. During surgery, subjects again received taped messages at F_E' of 1.0 and 1.4 MAC (order randomized). Two of the three messages consisted of 5 questions plus the associated answers. After 24 h the questions were again asked with multiple choice answers provided. Twelve controls underwent similar surgery and anesthesia but heard the answers to 10 questions before, rather than during anesthesia.

RESULTS; Study and control subjects did not differ in age, weight, type of surgery and duration of anesthesia. The number of questions (out of 5) answered correctly post-operatively was 1.5±1.1 for questions answered during 0.6MAC anesthesia, 1.2±.8 for questions answered during 1.0MAC anesthesia, 1.2±1.0 for questions answered during 1.4MAC anesthesia, and 1.0±.9 for unanswered questions (means±SD, $P > 0.05$). Control subjects answered 9.7±0.5 questions correctly out of 10 whose answers had been presented compared to 0.8±1.1 out of 5 unanswered questions ($P < 0.05$).

CONCLUSION; We found a trend indicating that learning of auditory information may occur at light levels of anesthesia, but this trend did not approach statistical significance. The present studies are ongoing and will provide results from a larger group.

1.Lancet August 27 1988;491.
2.Br J Anaesth 1985; 57:174-179.
3.Anaesthesia 1987; 42: 596-603.

S61

TITLE: DIRECT COMPARISON OF ETOMIDATE & PROPOFOL ON SYMPATHETIC NEURAL OUTFLOW & BAROREFLEX FUNCTION IN MAN

AUTHORS: T.J. Ebert, M.D., Ph.D., R.J. Berens, M.D., M. Muzi, M.D., J.P. Kampine, M.D., Ph.D.

AFFILIATION: Department of Anesthesiology, Medical College of Wisconsin and VA Medical Center, Milwaukee, WI 53295

Bolus administration of propofol can lead to marked hypotension. The mechanism(s) of this response has been attributed to reductions in cardiac output and/or peripheral resistance. In contrast, etomidate induction results in a relatively stable hemodynamic profile. In the present research, approved by the Human Studies Committee, continuous recordings of efferent muscle sympathetic nerve traffic (MSNA) from the peroneal nerve were evaluated before and after induction with propofol. These were compared to MSNA responses during induction with etomidate.

Arterial pressure, forearm vascular resistance (FVR, plethysmography), HR and MSNA were evaluated in 8 unpremedicated patients receiving propofol (2.5 mg/kg) and 6 receiving etomidate (0.3 mg/kg) after 10 ml/kg of IV saline. Baseline hemodynamics, MSNA and baroreceptor gain (reflex tachycardia and increases in MSNA during a 100 μg bolus of nipride) were similar between groups while awake. Average data are shown in the table. Etomidate induction did not significantly alter any measured parameter.

	Etomidate		Propofol		
	Awake	Asleep	Awake	Asleep	
R-R interval, msec	1003 ±59	907 ±77	977 ±48	786 ±34	*+
MAP, mm Hg	96 ±2.2	107 ±6.1	86 ±3.8	72 ±5.0	*+
FVR, units	22.6 ±2.1	19.2 ±2.6	26.6 ±4.7	19.0 ±4.3	*+
MSNA, bursts/100 cardiac cycles	40 ±9	30 ±6	25 ±4	4 ±2	*+
Baroreceptor Gain (Slopes)					
Cardiac, msec/mm Hg	9.1 ±1.5	7.7 ±2.5	12.5 ±2.5	6.6 ±1.9	*+
Sympathetic, bursts/mm Hg	-3.6 ±0.3	-3.1 ±0.4	3.6 ±0.4	1.1 ±0.6	*+

Means ± SEM. * = $p<0.05$, significant change from awake baseline; + = $p<0.05$, different response compared to etomidate.

Thus hypotension during propofol induction is due, in part, to inhibition of sympathetic vasoconstrictor outflow and a reduced ability of the baroreceptors to respond to the hypotension. In contrast, etomidate did not reduce MSNA and maintained hemodynamic stability which may be due to preserved baroreceptor function.

S62

Title: **SHOULD MONOAMINE OXIDASE INHIBITORS BE DISCONTINUED PREOPERATIVELY?**

Authors: **Z. Ebrahim, M.D., J. O'Hara, M.D., J. Tetzlaff, M.D.**

Affiliation: The Cleveland Clinic Foundation; Cleveland, Ohio

Introduction. Monoamine oxidase inhibitors (MAO) have long been considered a contraindication to elective surgical procedures under anesthesia. We retrospectively reviewed the anesthesia records of patients suffering from rheumatoid arthritis (RA) who had elective surgery while on MAO inhibitors.

Methods. The medical records of 1,000 patients scheduled for joint replacement due to RA between 1973-1976 were reviewed. Factors such as age, sex, number of anesthetics, preoperative medication, induction agents, intraoperative blood pressure measurements, postoperative complications and length of recovery room stay were examined. Ten male and 22 female patients between the ages of 41 to 77 who were on a regimen of isocarboxazid 10 mg daily for greater than a month had a total of 51 anesthetics. Premedication consisted of combinations of demerol, morphine, atropine and vistaril. Forty-six general anesthetics and five regional anesthetics were administered. Induction agents were either thiopental or ketamine. Maintenance anesthesia was an inhalational anesthetic with or without a muscle relaxant and supplemental narcotic in some cases.

Results. Mean arterial pressure changes from baseline lasted less than 10 minutes. Five patients had intraoperative hypotension for periods of 10 to 20 minutes (MAP 30% < preop). These patients responded with fluids, surgical stimulation, and methoxamine (in one patient). Hypertension (MAP 30% > preop) for a 10 minute period was recorded in one patient. The remaining changes in MAP were less than 5 minutes in duration. Four patients were bradycardic (HR 40-45) requiring a single dose of atropine. Postoperatively there were no major complications as a result of the anesthetic MAO interaction. The recovery room stay of these patients was no different from the patients not on MAO inhibitors.

Discussion. Patients on MAO inhibitors are probably still the only group of patients that anesthesiologists are reluctant to anesthetize because of a possible adverse drug reaction. Earlier case reports were of cardiovascular and central nervous system interaction manifesting in hemodynamic instability and hypethermia. Recent reports [1-4] suggest that patients on MAO inhibitors can be anesthetized safely for elective procedures without discontinuing the drug. Current anesthesia practice and standard references still caution against administering an anesthetic to a patient unless the MAO inhibitors have been discontinued for 2 weeks. In our study no patient suffered any untoward effect as a result of an interaction between an MAO inhibitor and commonly used anesthetic agents and narcotics. However, while the regimen of isocarboxazid 10 mg daily was probably a low dose, some patients did receive demerol and did not exhibit any adverse symptoms. We feel that patients on MAO inhibitors should not be routinely cancelled for elective surgery. Patients on a low dose MAO inhibitor with appropriate selection of anesthetic drugs and monitoring can be safely anesthetized.

References.

1. JAMA 260:3507, 1988.
2. Can J Anaesth 36:1, 64-74, 1989.
3. Br J Anaesth 60:222-227, 1988.
4. JAMA 261:3407, 1989.

S63

TITLE: **MULTIPLE DOSE EVALUATION OF THE EFFICACY OF OCFENTANIL HCl (A-3217) TO PRODUCE POSTOPERATIVE ANALGESIA**

AUTHORS: Z. EBRAHIM, M.D., P. Schoenwald, M.D., M. Grimes-Rice, R.N.,B.S.N., M.C. Damask, M.D.*, P.A. Khairallah, M.D.
AFFILIATION: The Cleveland Clinic Foundation, Cleveland, Ohio; *Anaquest, Division of BOC Inc.

Ocfentanil, a naloxone-reversible piperdine derivative, has been reported to produce analgesia for 20 to 40 min [1]. The purpose of this study was to evaluate the safety and effectiveness of Ocfentanil for postoperative pain relief in conscious patients in the postoperative care unit (PACU).

The protocol was approved by the IRB and informed consent was obtained from all patients. Sixty ASA I and II patients were enrolled in this prospective double-blinded, randomized, controlled study and assigned to four groups of 15 each. The three ocfentanil groups received 0.1 mcg/kg, 0.5 mcg/kg and 0.75 mcg/kg doses, respectively. The fourth group received morphine 0.07 mg/kg. Fentanyl up to 2.5 mcg/kg was used on induction and isoflurane and nitrous oxide were used for maintenance anesthesia. Each patient's pain was evaluated by the visual analog pain score scale (0 to 10), a verbal rating scale (none to excruciating), and a sedation rating scale. This evaluation was done prior to administration of the study drug and then at 5, 10, 15, 30 and 60 minutes afterward. Blood pressure, EKG, heart rate, respiration and SaO_2 were monitored during the study. Patients were withdrawn from the study and medicated if at any point during the assessment their pain had not improved or increased.

Analgesia in Group 1 was only adequate in 3/12 patients at the end of an hour. While pain relief in the three other groups was satisfactory and showed no significant differences between the groups when evaluated by student's T-test. Four patients in the morphine group had EKG changes and two of them required treatment (Table 1). No other differences were noted in the study.

Ocfentanil in a dose of 0.5 to 0.75 mcg/kg produced safe and effective analgesia, and was just as effective as morphine 0.07 mg/kg for postoperative pain relief. While as previously reported [1], analgesia with this dose of ocfentanil may last 20 to 40 minutes, approximately 50% of patients in our study had postoperative pain relief that lasted up to an hour (Fig. 1).

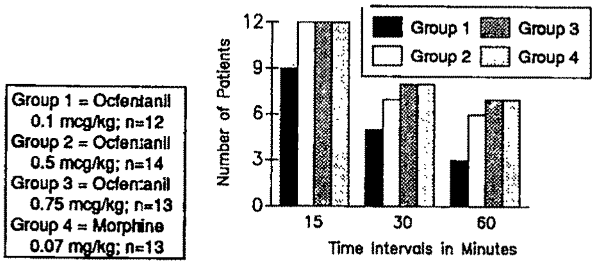
1. Glass P, et al.: Anesthesiology 71:A321, 1989.

Table 1
ADVERSE EFFECTS IN PACU

	Group 1	Group 2	Group 3	Group 4
Nausea	3[a]	2[a]	2[b]	3
Bradycardia	0	0	0	2[c]
Arrhythmia	0	0	0	2[d]

a=Abdominal Surgery
b=Nausea before and after drug administration
c=Required treatment
d=Not treated, resolved spontaneously

Figure 1



S64

TITLE: SINGLE-LUMEN TUBE FOR TWO-LUNG AND ONE-LUNG VENTILATION DURING THORACIC SURGERY

AUTHORS: N. El-Baz, M.D., L. Faber, M.D., F. Kittle,M.D., W. Warren,M.D.,
AFFILIATION: Anesth.and CV&Thoracic Depts.,Rush Medical College; Chicago, IL 60612

The use of single-lumen tubes (SLT) for airway control during thoracic surgery were evaluated in this study. We examined 2 methods for endobronchial intubation and gas exchange during right lung ventilation (RLV) and left lung ventilation (LLV).

We studied, in a retrospective fashion, 120 patients receiving two-lung (TLV) and one-lung ventilation (OLV) during a variety of intrathoracic surgical procedures. After induction of anesthesia, a cuffed SLT (7.5mm I.D., 32cm long, National catheter) was placed in the trachea and initially used for TLV. Intraoperatively, selective OLV was achieved by advancement of the tube into the bronchus of the dependent (healthy) lung.

Endobronchial Intubation

Method	#	Advantages
Fiberoptic bronchoscopy	80	airway visualization
Bronchial compression	40	rapid, no equipment

The change from TLV to OLV was associated with a significant drop in PaO_2 in all patients. Patients were divided into 2 equal groups (A & B) according to the lung ventilated. Gas exchange during RLV was not significantly different from that during LLV (FIO_2=1.0).

Group	#	PaO_2	O_2 Sat.	PvO_2	Qs/Qt
A. Right lung	60	178	98	51	37
B. Left lung	60	176	98	49	41

Mixed venous gases and Qs/Qt in A were not significantly different from those obtained in B.

Ten patients in A had a mean PaO_2 below 100mmHg compared to 6 patients in B.

Group	#	PaO_2 (Range) mmHg
A. RLV	10*	86 (69-97)
B. LLV	6	90 (78-99)

PaO_2 below 100mmHg was measured at least once in 30 patients in A, compared to 28 patients in B. The lowest measured PaO_2 in these patients was:

Group	#	Lowest PaO_2 mmHg
A. RLV	30	76 (53-96)
B. LLV	28	77 (58-99)

In these 58 patients, oxygen saturation was once measured below 90% in 4 patients in A and 2 patients in B. In these 6 patients, the tube was withdrawn into the trachea for TLV. After improvement of oxygenation, the tube was readvanced and OLV maintained adequate oxygenation.

After surgical resection, the tube was withdrawn into the trachea and the resumption of TLV was associated with significant improvement of oxygenation in all patients.

RLV and LLV through SLT provided adequate gas exchange in all patients and was similar to that reported during the use of double lumen tubes or endotracheal tube/endobronchial blocker combination. SLT allows for the use of an adult fiberoptic bronchoscope which improves the safety of intubation, anesthesia and OLV during thoracic surgery.

S65

Title: THE EFFECT IN THE PARTURIENTS OF EPIDURAL CATHETERS, LIDOCAINE TEST DOSE AND FENTANYL

Authors: M. El-Naggar, MD, M. Mathew, MD, J. Dalisan, MD, R. Kartha, MD
Affiliation: Anesthesia Dept., Cook County Hospital, Chicago, IL 60612

Introduction: This study was aimed to examine the role of insertion of epidural catheters and the injection of 3cc lidocaine 1.5% with 15μg epinephrine as test dose (TD) in modulating labor pain and the interaction of the TD with epidural fentanyl.

Methods: After institution approval and patients' consent, the effects of insertion of epidural catheters and the administration of a TD were evaluated in 22 parturients while the interaction between the TD and the epidural injection of 100μg fentanyl in 10cc preservative free saline (F) was studied by randomly assigned parturients to one of the following groups: Group 1 (G1) received F without the TD (N:13); Group 2 (G2) received the TD and then F when the effect of the TD was receding (N:15), and Group 3 (G3) received the TD followed immediately by F (N:12). The vital signs were recorded, and the symptoms and signs of discomfort and the patients' perception of labor pains were evaluated by a blinded observer using a linear analog scale (0 to 10) until either 5cc B 0.25% was given or delivery. ANOVA test and multivariate analysis of variance followed by Dunnett's test were used to analyse the data; $P<0.5$ was significant.

Results: Demographic, obstetrical and neonatal variables were equally distributed and there were no significant changes in the blood pressure or pulse rate ($P>0.05$). There were no significant changes in the discomfort and pain scores 5-10 minutes after insertion of the epidural catheters ($P>0.05$). After the TD, there was a significant improvement in patients discomfort ($P<0.0001$) and pain scores ($P<0.0001$) that lasted 39±37 minutes. There was no significant difference between G2 and G3 in regards to scores of discomfort or pain, duration of analgesia, or frequency of B administration ($P>0.05$); however, there was significant differences in all these variables when G2 or G3 were compared to G1 ($P<0.05$). Also, there was a significant difference in these variables between G2 or G3 in comparison to the combined effect of the TD and of F in G1 ($P<0.05$). Although the changes in discomfort and pain scores after F in G1 were significant ($P<0.05$); however, clinically they were of high magnitude, short duration and significantly less than those after the TD.

Conclusions: A) The insertion of epidural catheters had no placebo effect in parturients eligible for epidural analgesia; b) the TD modulated labor pain; c) epidural F without TD was ineffective in relieving labor pain; d) epidural F given immediately after the TD or when its effect was receding provided significant improvement in labor pain; and e) the interaction between F and the TD was that of potentiation.

S66

Title: ISOLATION OF PERIPHERAL AND CENTRAL THERMAL COMPARTMENTS IN VASOCONSTRICTED POSTOPERATIVE PATIENTS

Authors: M H Ereth, M. D., D I Sessler, M.D.*, and R L Lennon, D. O.
Affiliation: Department of Anesthesiology, Mayo Clinic, Rochester, MN; *Department of Anesthesia, UCSF, CA

Introduction. Large changes in peripheral blood flow only minimally alter cutaneous heat loss.[1] Thermoregulatory vasoconstriction may primarily separate peripheral and central thermal compartments, providing a thermal buffer for central temperature. Limited heat transfer between the compartments may contribute to the observed difficulty in warming surgical patients. We tested the hypothesis that cutaneous warming does not rapidly increase central temperature in vasoconstricted postoperative patients.

Methods. With IRB approval and informed consent, 12 healthy patients who were hypothermic following hip arthroplasty were studied. During recovery from a midazolam, fentanyl, and vecuronium anesthetic, they were randomized to receive cotton blankets (control) or convective warming with a Bair Hugger®. Cutaneous heat flux differs by ≈ 115 watts between these treatments.[2] Oxygen consumption, mean skin temperature, and pulmonary artery temperature were measured. Vasoconstriction was defined as a forearm-fingertip gradient ≥ 2°C.

Results. During recovery, all patients vasoconstricted. No postanesthetic tremor was observed. Oxygen consumption averaged 2.6 ± 0.8 ml/kg/min in control and 3.1 ± 1.2 ml/kg/min in those actively warmed (P=.11). Mean skin temperature was significantly higher in actively warmed 35.1 ± .8°C, than in control patients, 33.4 ± .6°C, (P=.00). Pulmonary artery temperature was similar (fig. 1).

Discussion. In humans with normal heat production given convective warming, mean body temperature would be expected to increase ≈1.3 C/h.[3] The significantly different mean skin temperature and similar pulmonary artery temperature suggest that peripheral to central flow of heat is limited in vasoconstricted patients. We conclude that 90 min of cutaneous heating does not significantly increase central temperature in vasoconstricted postoperative patients. In contrast, cutaneous warming of vasodilated patients during surgery is remarkably effective.

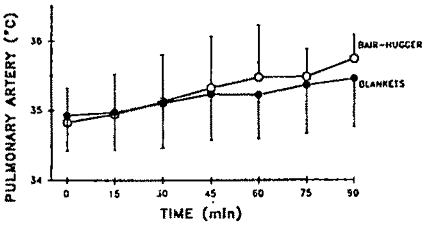


Figure 1. Mean (± SD) pulmonary artery temperature during recovery. There were no significant differences between groups.

References. 1. Sessler, DI et al. Thermoregulatory vasoconstriction minimally decreases cutaneous heat loss. Anesthesiology, in press.
2. Sessler DI, Moayeri A. Skin-surface warming: Heat flux and central temperature. Anesthesiology, in press.
3. Burton AC, J Nutr 1985;9:261-280.
4. Kelley SD et al. Forced air warming minimizes hypothermia during orthotopic liver transplantation. Anesthesiology, in press.

Supported by Augustine Medical, Inc. and National Institute of Health grant #R29 GM39723.

S67

Title: SPINAL CORD IMAGING WITH TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Authors: M.H. Ereth, M.D. and P.E. Stensrud, M.D.
Affiliation: Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905

Introduction: Maintenance of spinal cord integrity is a major goal during anesthesia for repair of the thoracic aorta. Various methods, including vascular shunts, pharmacologic interventions, and cerebrospinal fluid drainage are used to maximize spinal cord perfusion. No direct method exists to monitor spinal cord perfusion intraoperatively. Funck, et al have reported imaging of the spinal canal with transesophageal echocardiography (TEE).[1] Such images may be useful to evaluate changes in spinal cord perfusion that occur when the aorta is cross-clamped. The present study was conducted to determine the feasibility of visualization of the spinal cord by intraoperative TEE.

Methods: Following IRB approval and informed consent, TEE imaging of the spinal cord was attempted in 17 adult patients undergoing coronary or valvular heart surgery. A 5.0 MHz imaging probe was used. Following induction of anesthesia, the TEE probe was placed in the midesophagus. After obtaining baseline images of the heart, the TEE probe was rotated 180 degrees within the esophagus. Imaging of the spinal canal was achieved by directing the ultrasound beam perpendicular to the spinal cord through the intervertebral discs. Beginning at the level of the aortic valve, advancing or retracting the TEE probe provided imaging of successive spinal cord segments. Videotape recordings of 2-dimensional and M-mode echocardiographic images were made which included superimposed electrocardiogram and radial artery waveforms.

Results: Imaging of the spinal cord with TEE was achieved in 100% of patients. The distance of the probe from the teeth during spinal cord imaging ranged from 14 to 42 cm. Most easily visualized were the lower cervical to midthoracic levels. Between 2 and 13 vertebral segments were identified (mean of 6.5). Pulsations of the spinal canal contents in synchrony with the arterial pressure waveforms were noted in all patients. These pulsations were distinct from probe motion caused by the proximity of the probe to the heart. In 6 patients, pulsation of the anterior spinal artery could be seen in 2-dimensional and M-mode formats.

Discussion: The observed motion of the spinal cord results from the combination of vascular pulsation and transmitted cerebrospinal fluid (CSF) pressure waves. The pressure waves result from displacement of intracranial CSF secondary to increased intracranial blood volume during systole. The results of this feasibility study suggest merit and the need for additional work to develop optimal imaging techniques. It would be of value to use higher frequency ultrasound and low velocity Doppler measurements to further delineate the relative contribution of vascular pulsation and CSF pressure waves. Additional studies may then be directed to preservation of the vascular pulsation component during thoracic aortic surgery. Whenever possible, imaging of the spinal cord below the zone of the aortic cross-clamp may provide information on the integrity of spinal cord perfusion in thoracic aortic surgery.

Reference:

1. Dtsch Med Wschr 114:529-533, 1989

S68

TITLE: PHRENIC ARTERY BLOOD FLOW DURING SINGLE TWITCH STIMULATION OF THE DOG DIAPHRAGM

AUTHORS: R.F. Erian, M.D.
AFFILIATION: Dept. of Anesth., Univ. Texas Health Science Center, San Antonio, TX 78284-7838

Introduction: It is thought that single twitch (ST) stimulation every 10 sec is a better mode of stimulation to monitor the onset of action of neuromuscular blockers, because of lack of effect on muscle blood flow. It has recently been shown that TOF stimulation of the diaphragm increases phrenic artery blood flow more than two-fold.[2] It is unclear if ST stimulation has any effect on muscle blood flow. We, therefore, studied the effect of ST stmulation of the diaphragm on phrenic artery blood flow.

Methods: This study was approved by our institutional animal care committee. Seven mongrel dogs (weight: 30-40 kg) were anesthetized with pentothal 10 mg/kg at induction and halothane 1% during maintenance. All animals were supine, intubated, and mechanically ventilated. PO_2 and $PaCO_2$ were maintained at > 60 mmHg and between 35-40 mmHg, respectively. TOF stimulation of the diaphragm was achieved using a transvenous pacing catheter connected to a Grass S48 stimulator delivering supramaximal square wave impulses of 2 msec (a frequency of 1 Hz for 1 sec every 10 sec). Isometric contraction of the diaphragm was assured by binding the lower chest and abdomen with a cast. Blood flow to the diaphragm was estimated using a doppler flow probe of appropriate size around the left phrenic artery (flat to 20 MHz).

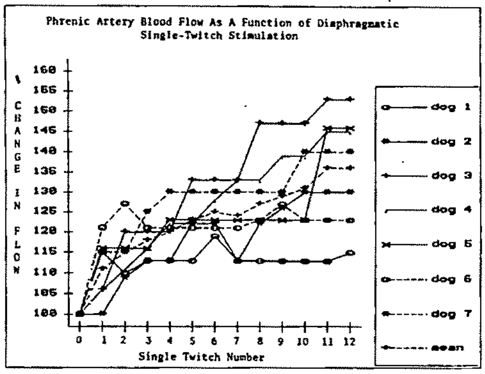
Results. Heart rate, blood pressure, acid-base status, temp and Pdi were constant throughout the experimental period. The graph depicts phrenic artery blood flow as a function of a twitch number for 7 dogs and mean values. By the fourth twitch, mean blood flow had increased by 20% ($p < 0.03$). By the 12th twitch mean blood flow seemed to have reached a plateau with a maximum increase of 36% ($p < 0.01$).

Discussion: Single-twitch (ST) stimulation of the diaphragm increases phrenic artery blood flow by 36%. This increase was progressive and did not seem to reach a plateau until about 2 min of stimulation. Since an increase in blood flow will affect the onset time of neuromuscular blockers, ST stimulation may also influence onset time. The significance of the effect of ST on onset time will depend on whether the increase in blood flow of peripheral muscles to ST stimulation is of the same magnitude and also whether a 36% increase in neuromuscular blockers delivery will reduce onset time significantly.

Conclusion: ST stimulation increases muscle blood flow to the diaphragm and thus could potentially affect onset times of neuromuscular blocking drugs, in the diaphragm and other muscles.

Reference

1. Can J Anaesth 37:S162, 1990.



S69

Title: EFFECT OF HALOTHANE ON SLOWLY INACTIVATING Na+ CURRENT IN CANINE CARDIAC PURKINJE CELLS.

Authors: H Eskinder, PhD, F Supan, PhD, LA Turner, MD, JP Kampine, MD, PhD, and ZJ Bosnjak, PhD
Affiliation: Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI 53226

In cardiac Purkinje fibers Na^+ channel currents have a fast and slow component. The fast Na^+ current is responsible for the upstroke of the action potential (AP) while the slow component ($_sI_{Na}$) plays an important role in the plateau phase of the AP. $_sI_{Na}$ is sensitive to low doses of tetrodotoxin (TTX) resulting in decreased action potential duration (APD) without reduction of V_{max} in cardiac Purkinje cells.[1] Even though a reduction of extracellular Ca^{++} concentration usually prolongs APD in Purkinje cells, halothane decreases Ca^{++} channel currents[2] and also APD in these cells.[3] The direct effect of halothane on $_sI_{Na}$ has not been well documented. Therefore this study examined the effects of halothane on $_sI_{Na}$ in single canine cardiac Purkinje cells.

After institutional approval, false tendon Purkinje fibers from dog heart were incubated at 37°C for 3-4 hrs in Ca^{++} free collagenase solution. The digested fibers were washed and placed in a perfusion chamber containing normal Tyrodes solution and voltage-clamped with a patch pipette filled with 70 mM Cs glutamate and 60 mM CsCl. Nifedipine (1 μM) and Ni^{++} (40 μM) were added to the external solution to block the inward Ca^{++} current and veratridine (0.5 μM), a Na^+ channel agonist, was used to enhance the slowly inactivating component of the Na^+ channel current. Na^+ channel current was elicited by depolarizing pulses (400 ms) from a holding potential of -100 mV to stepwise (10 mV increments) more positive membrane potentials. We analyzed the amplitude of TTX- sensitive Na^+ current at 200 msec pulse duration before, during and after the introduction of halothane (0.4 and 0.8 mM).

Figure 1 shows the effect of halothane on $_sI_{Na}$ at 200 msec from the beginning of the pulse. Slowly inactivating Na^+ current, elicited during progressive depolarization from a holding potential (HP) of -100 mV showed threshold activation around -80 mV and peak activation around -60 to -50 mV. This current was blocked by TTX (10 μM, not shown). Halothane, in a concentration-dependent manner, depressed the amplitude of $_sI_{Na}$ in the entire voltage-range studied. Representative tracings showing the effect of halothane (0.8 mM) on $_sI_{Na}$ elicited by depolarizing pulses (400 ms) from an HP of -100 to -40 mV are shown in Figure 2. Halothane significantly suppressed the current amplitude.

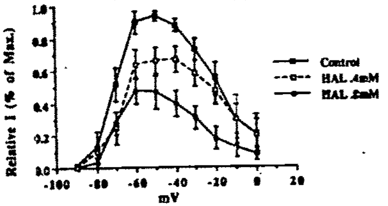


Figure 1

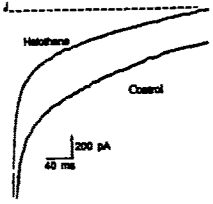


Figure 2

The results of our experiments indicate that halothane suppresses the $_sI_{Na}$. Reduction of $_sI_{Na}$ by halothane may contribute to the decreases of APD produced by halothane[3] and decreases in functional refractory period for propagation of His bundle extra stimuli in the canine heart in *vivo*.[4]

References: 1) *Am J Physiol* 236:H561-H567, 1979; 2) *Biophysical J* 57(2):518a,1990; 3) *Anesthesiology* 67:619-629, 1987; 4) *Anesth Analg* 59:327-334,1980

S70

Title: PULMONARY AND SYSTEMIC HEMODYNAMICS, ECG AND BLOOD GAS CHANGES WITH USE OF A PNEUMATIC TOURNIQUET.

Authors: N.R. Fahmy, M.D., D. Patel, M.D., N. Sunder, M.D.
Affiliation: Departments of Anesthesia and Orthopaedic Surgery, Harvard Medical School at the Massachusetts General Hospital, Boston, MA 02114

Despite the extensive use of a pneumatic tourniquet to obtain a bloodless operating field during operations on the extremities, detailed studies of its effects on the circulation are lacking. We report the changes in the pulmonary and systemic circulations, electrocardiogram, and blood gases before, during and after application of a pneumatic tourniquet for lower extremity procedures.

Twenty ASA I-III patients, ages 22 to 74 years, gave informed consent to an institutionally approved protocol. They were scheduled for knee arthrotomy (n - 7), total knee replacement (n - 9), or tibial osteotomy (n - 4). There was ECG evidence of myocardial ischemia in 5 patients, and of an old myocardial infarction in another three patients. All eight patients were receiving a beta blocker, nitroglycerin, or a calcium entry blocker. All patients received general endotracheal anesthesia using halothane or enflurane, $N_2O:O_2$, muscle relaxants, and increments of fentanyl as required. Pulmonary and systemic arterial pressures, cardiac output (thermodilution), heart rate, and arterial blood PO_2, PCO_2, and pH were measured before and during tourniquet application, and after release of the tourniquet. The pneumatic cuff pressure was 350 mm Hg for 115 to 127 minutes.

Pulmonary and systemic arterial pressures increased significantly 45 min after tourniquet application. Pulmonary wedge pressure increased from 11±2 to 29±5 mm Hg ($P < 0.01$). ECG evidence of worsening myocardial ischemia developed in 3 of the patients with known coronary artery disease (CAD). Infusion of nitroglycerin reversed these changes. Release of the tourniquet, and for 15 minutes thereafter, was followed by a significant reduction in pulmonary and systemic pressures and a significant increase in cardiac output. Arterial PO_2 and pH decreased and PCO_2 increased significantly.

Use of the pneumatic tourniquet is associated with important changes in the pulmonary and systemic circulations. Such changes can be particularly hazardous in patients with CAD. Worsening of myocardial ischemia occurred in 3 patients, which necessitated the infusion of nitroglycerin. Another patient (not in the study) developed an acute myocardial infarction (confirmed by enzymes) during tourniquet application. Increased pulmonary arterial pressure may help explain deterioration of oxygenation in patients with ventricular septal defect. The elevation of $PaCO_2$ following release of the tourniquet causes further increases in intracranial pressure in patients with head injury (two patients). A pneumatic tourniquet should be used with caution in patients with CAD and, based on our experience, in patients with intra-cardiac shunts and those with elevated intracranial pressure.

S71

HEMODYNAMIC EFFECTS OF PENTAMORPHONE FOR CARDIAC ANESTHESIA IN MAN

B Falinski MD, A Klochany MD
PS Sebel MB, CC Hug Jr MD

Department of Anesthesiology
Emory University Medical School, Atlanta GA

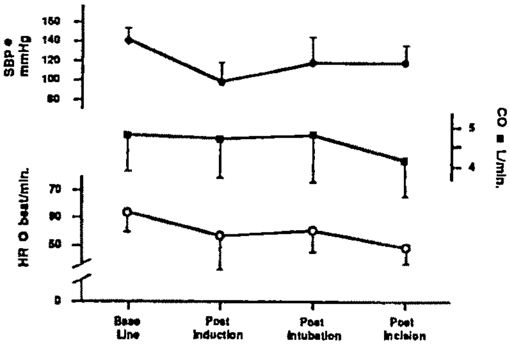
Pentamorphone (P) is a morphinan derivative 500 times more potent that morphine.(1) P 1.0 μg/kg has a duration of action and efficacy similar to fentanyl 5 μg/kg.(2) This study assessed P as the sole anesthetic for patients undergoing coronary artery surgery.

Ten consenting patients (61±5.7 yr, 83±9.7 kg) received 2 mg lorazepam. After monitor placement and vecuronium 1 mg, P 2 μg/kg/min was infused until loss of consciousness (LOC). Succinylcholine 1.5 mg/kg was given for endotracheal intubation. Up to 2 doses of P (1/10 induction dose, first 2 patients; 1/2 induction dose 8 patients) were given for responses to noxious stimulation, and if uncontrolled by P, enflurane was added. Hemodynamic variables were recorded continuously except cardiac output (CO) and pulmonary artery occlusion pressure (PAOP) which were measured intermittently. Data are mean ± SD; statistical analysis was by one-way repeated measures ANOVA.

P 5.1 ± 1.6 μg/kg produced LOC; supplements averaged 4.5 ± 2.5 μg/kg. Six patients required enflurane. LOC was accompanied by a reduction in heart rate and 12-63 mmHg reduction of systolic BP. PAOP and CO were unaffected. Mean BP below 60 mmHg occurred in 5 patients, 3 of whom required vasopressors.

P produced effects typical of large doses of an opioid. Hypotension without reduction in CO or PAOP suggests that P reduced SVR. P offers no advantage over opioids currently available for use in a high dose technique.

REFERENCES: 1. Anesth Analg 68:302, 1989. 2. Anesthesiology 71:A225, 1989.



S72

TITLE: NICARDIPINE AUGMENTS CARDIOVASCULAR HEMODYNAMICS DURING DELIBERATE HYPOTENSION IN DOGS

AUTHORS: R. Fischer,M.D., B. Braverman,Ph.D., R.McCarthy,Pharm.D.,A.Ivankovich,M.D.
AFFILIATION: Anes.Dept.,Rush Medical College, Chicago, IL

Nicardipine (NIC), a new calcium channel antagonist (CCA), has protective effects on the ischemic myocardium. Sodium nitroprusside (SNP) is commonly used for deliberate hypotensive anesthesia, but it has been associated with adverse effects during myocardial ischemia in humans. The present study was performed to evaluate coronary, hemodynamic, and renal effects of NIC compared to SNP during deliberate hypotensive anesthesia in dogs.

After approval by our institutional animal care committee, 20 mongrel dogs were studied. Baseline HR, ECG, MBP, LAP, LVEDP, CV pressures, and CO, coronary (CBF) and renal (RBF) blood flows. Coronary sinus lactate, serum electrolytes, and creatinine were obtained. After two 15-min renal clearance periods, controlled hypotension with either intravenous SNP (n=11: .5-3 ug/kg/min) or NIC (n=9: bolus 125 ug/kg and infusion .5 ug/kg/min). MBP was maintained at 60mmHg during the 60 min hypotension period. SNP or NIC was discontinued and an additional observation was made after 60-min. Hemodynamic data was assessed by two-way analysis of variance with repeated measures in one variable (time). P< 0.05 was considered statistically significant.

RBF decreased significantly with hypotension. Only 3 of 9 dogs given NIC produced urine during the drug infusion period, whereas 10 of 11 SNP-treated dogs did. Renal function (GFR, fractional excretion of electrolytes) in NIC dogs was similar to those receiving SNP. 2 of 9 dogs given NIC developed bradycardia and an A-V conduction block during the drug infusion. Coronary lactate extraction did not differ.

The results of this study indicate that NIC may present advantages (see table) during deliberate hypotensive anesthesia as compared to SNP. RBF was similar between the drug groups, but the large number of NIC animals failing to make urine was unexpected, as was the bradycardia and heart block following NIC administration. Because of its advantageous cardiovascular effects, nicardipine may be an attractive adjunct for inducing hypotensive anesthesia. Further studies are underway to determine if improved dosage schemes can be developed.

	CONTROL		DRUG INFUSION		1HR POST-INFUSION	
GROUP	I	II	I	II	I	II
MBP (mmHg)	81(15)	84(14)	55(8)+	60(9)+	82(16)	66(5)*+
LAP (mmHg)	7(2)	8(2)	6(2)	10(3)*+	6(2)	9(3)
LVEDP(mmHg)	2(2)	3(3)	1(1)	6(4)*+	2(2)	5(3)*
HR (b/min)	112(13)	122(22)	110(12)	88(25)*+	106(15)	96(32)+
CVP (cm H_2O)	2(1)	2(1)	2(1)	2(1)	2(1)	2(1)
SVR (units)	2598 (1037)	2767 (1136)	3101 (2071)	1735* (544)	4368+ (1587)	2099* (680)
CO (L/min)	2.6(0.6)	2.7(0.9)	1.7(0.7)+	2.8(0.8)*	1.6(0.6)+	2.7(0.9)*
CBF (ml/min)	46(23)	33(15)	25(19)+	20(12)	33(27)	21(13)*
CVR (units)	146 (87)	479* (793)	251 (286)	150+ (69)	374 (461)	219+ (195)
$\dot{V}$ (ml/min)	1.6(1.1)	0.5(0.4)	0.2(0.2)	0.1(0.1)	0.5(0.6)	0.3(0.4)
RBF (ml/min)	191(65)	222(124)	124(59)+	97(93)+	138(51)	120(94)+

Values presented as Mean(SD)
* p<.05 Between groups at time period
+ p<.05 Within group vs Control

I = SNP
II = NIC

S73

Title: DOES ADDITION OF EPINEPHRINE DELAY VOIDING OR ENHANCE CAUDAL ANALGESIA IN CHILDREN?

Authors: Q. Fisher MD, E. Spurrier MD, G. Boltz MD, C. McComiskey RN, B. Beaver MD, J. Hill MD,
Institution: UNIVERSITY OF MARYLAND, BALTIMORE, MD

Introduction. Regional anesthesia is commonly used for adjunctive analgesia in pediatric surgery of the perineum and lower abdomen. Although a variety of blocks are effective, conclusions regarding urinary retention and duration of effective analgesia remain controversial[1]. Statements about delay in micturition in particular, have been made without reference to fluids administered[2,3].

This institutionally approved study sought to compare the duration of analgesia and time to micturition when adequate hydrating amounts of fluid were administered to children receiving ilioinguinal or caudal block with and without epinephrine.

Methods. With informed parental consent, children aged six months to 10 years scheduled for elective herniorrhaphy or orchiopexy were randomly assigned to receive one of three blocks at the end of surgery, using 0.25% bupivacaine: Caudal, 0.75cc/kg (C/-); Caudal with epi 1:200K, 0.75 cc/kg (C/+); or Ilioinguinal-iliohypogastric with epi 1:200K, 0.4cc/kg per side (ILIH). All patients had general anesthesia with O_2-N_2O-halothane, and were given intraoperative D_5-Ringer's Lactate equivalent to 6 hours maintenance. Postoperative fluids were allowed ad. lib. Pain scores[4] were assessed at 30 minutes postoperatively, and then hourly until discharge. A follow-up phone interview was conducted by one observer for all patients 24 hours postoperatively. Time of first void was noted by nursing staff or parents. Parents, patients, nursing staff and the research observer were blinded to the type of block. Duration of analgesia was taken as the point at which an analgesic was required (pain score >6 or equivalent in the observer's judgement). Data were analyzed with ANOVA, chi-square, pairwise t-test, and Bonferroni correction where appropriate.

Results. The mean age of patients (3.1 ± 2.8 years) was not different among the groups. Caudal bupivacaine tended to produce longer times to micturition; with epi added this was significantly longer than ILIH. However, all but two patients voided within 8 hours; the other two voided at 8½ (C/-) and 10½ (C/+) hours postoperatively. There were no significant differences in the numbers requiring analgesics in the first twenty-four hours.

Conclusion. We conclude that caudal bupivicaine plain or with epinephrine, and ILIH are all effective in producing postoperative analgesia. Caudal block with epi significantly prolongs the time to postoperative voiding but not to a clinically important degree.

Group	Number	Time in min to first void (SD)	# Needing analgesics in 24 hr.
ILIH	18	172 (72)	13 (72%)
C/-	13	221 (143)	9 (71%)
C/+	16	292 (169) *	9 (56%)

*$p<.05$ compared to ILIH

1. ANESTH ANALG 1977;66:995-98
2. ACTA ANAES SCAND 1985;29:175-79
3. ANAESTHESIA 1986;41:1098-1103
4. ANESTHESIOLOGY 1987;66:832-34

S74

TITLE: PATIENT OUTCOME AND ANESTHESIA CARE DURING SEMI-EMERGENT INTUBATIONS OUTSIDE THE OPERATING ROOM

AUTHORS: SM Fisher, MD, TA Mickler, MD, L Chen, MD, JF Plate
AFFILIATION: Dept Anesthesia, Univ PA School of Medicine, Phila. PA 19104

Patients may require urgent intubations outside of standard anesthetizing areas. Previous studies have suggested a beneficial effect of specific pharmacologic adjuncts to facilitate endotracheal intubation.[1] This study was conducted to investigate whether the use of narcotics and other drugs at the time of semi-emergent intubation results in an increase in adverse outcome.

After approval by the Human Studies Committee, a retrospective review of patient medical records was conducted for the period of 1/1/87 to 6/30/87. Patients undergoing cardiopulmonary resuscitation were excluded. Data were analyzed by Fisher's exact test with $p<0.05$ considered significant.

Sixty-two intubations in 55 patients were performed by anesthesia residents (24 men; 31 women; age 19-47 yrs) in a variety of non-operating room areas: Medical Intensive Care Unit 45%, Emergency Room 29%, Surgical Intensive Care Unit 15%, and wards 10%. Of the 62 patients, 51 were orotracheally intubated and 11 were nasotracheally intubated. Altered mental status (23%), pulmonary edema (16%), pulmonary disease (16%), and accidental extubation (13%) accounted for the majority of the indications for intubation; more than 90% carried multiple diagnoses. Immediately prior to intubation 61% of patients received sedatives, 15% narcotics and 38% neuromuscular blocking (NMB) drugs.

There was no statistically significant difference between the administration of a sedative, narcotic or NMB drugs with postintubation hemodynamic instability. Immediate postintubation hypotension requiring therapy (Rx) with pressors, volume and/or Trendelenburg's position occurred 3 times as frequently in the group of patients who had received fentanyl (dose range 10-200 mcg) as compared to the total study group. Aspiration, defined by a new infiltrate on chest roentogram (CXR) within 48 hr occurred in 24% of patients but this was not associated with preintubation mental status, multiple laryngoscopies, or emesis at the time of intubation (Table).

Postintubation hemodynamic instability, and aspiration is not related to the use of pharmacological adjuncts. In spite of anecdotal reports, fentanyl was not shown to result in adverse circulatory responses in critically ill patients undergoing semi-emergent intubation.

Reference: 1. Fassoulaki A: Anesth Analg 68:112, 1989

TABLE: POSTINTUBATION MORBIDITY

	# Events
Hypotension requiring immediate Rx	7/62 (11.3%)
Hypertension requiring immediate Rx	4/62 (6.5%)
Multiple attempts at intubation	20/60 (33.3%)
48 hr CXR evidence of aspiration	15/62 (24.2%)
Survival to discharge	35/62 (56.5%)

S75

TITLE: Comparison of 24 Gauge Sprotte and 27 Gauge Quincke Needle on the Incidence of Post Dural Puncture Headache

AUTHORS: JF Flanagan, LCDR, MC, USNR, D Kumatta LT, MC, USNR, D Black, LT, MC, USNR
AFFILIATION: Department of Anesthesia, Naval Hospital, Oakland, CA

Post dural puncture headache (PDPH) is an all too frequent complaint associated with spinal anesthesia. The headache may be related to cerebrospinal fluid (CSF) leak at the dural puncture site (1). To minimize the likelihood of CSF leak, both smaller gauge needles and noncutting needle tips have been developed. We compared the incidence of PDPH in 224 patients using 24 gauge Sprotte (pencil point) needles and 27 gauge Quincke point needles (B-D).

METHODS: As part of a quality control and resident education process, patients receiving spinal anesthesia were evaluated at 72 hours post op. IRB approval was obtained for review of the data.

At the time of follow-up each patient was asked about he presence of headache during the post operative period. If a headache occurred, the severity was graded using a five point scale; 0= no headache, 1= minimal, nonpostural, 2= mild postural, not limiting daily activity, 3= moderate, postural, limiting normal daily activity, 4= severe, postural, bedridden, requiring analgesics (1).

RESULTS: 224 Consecutive spinal anesthetics were reviewed. 82 patients were treated with 27 gauge Quincke needles, 49 were male and 33 female. 142 patients were treated with 24 gauge Sprotte needles, 83 were male and 59 were female. Ages in both groups ranged from 18 to greater than 65 years. In the Sprotte needle group there were no headaches reported. In the Quincke needle group there were 3 headaches reported (3.7%). Two of the headaches occurred in female patients who underwent cesarean sections, their ages were 24 and 28 years. The remaining headache occurred in a 48 year old male undergoing hemorrhoidectomy. All headaches were classified as a 3 in severity. Using Yates Chi Square, no significant difference (p>.05) for headache occurrence between the two groups could be found.

DISCUSSION: Needle size, needle tip design, age and sex are important in the development of PDPH. If there is a direct relation between CSF leak and occurrence of headache, one would assume that a smaller gauge needle would result in a lower incidence of PDPH. This has been shown when different gauges of the same needle tip design have been compared (1,2).

In cadaveric dural studies the pencil point needle design has been shown to have a lower flow of CSF compared to the cutting needle design of the same gauge. However, a smaller gauge cutting needle had a slower flow rate of CSF than a larger gauge pencil point needle (3). This brings into question which is the most important factor; tip design or needle gauge?

In this paper we evaluated the incidence of PDPH using a 27 gauge Quincke needle and 24 gauge Sprotte (pencil point) needle. We found no significant difference between them. This would indicate that needle tip design is as important as needle gauge in the development of PDPH. Additionally, the 24 gauge needle was easier to use and had a more certain and rapid return of CSF.

TABLE

Needle	Male	Female
24 gauge	83	59
27 gauge	49	33

REFERENCES

1. Torutellotte W, Henderson W, Tucker R, Gilland O, Walker J, Koroman E. Headache (July) 73-78, 1982. 2. Dittmann M, Rankkl F. Anesthesiology 70: 1035-36, 1989. 3. Ready B, Cuplin S, Haschkke R, Nessly M. Anesth Analg 69: 457-60, 1989.

S76

TITLE: ACUTE EFFECTS OF CALCITONIN GENE-RELATED PEPTIDE ON NEUROMUSCULAR FUNCTION

AUTHORS: N.W. Fleming, M.D., Ph.D., D.A. White, M.D., B.K. Lewis, and K.L. Dretchen, Ph.D.

AFFILIATION: Department of Anesthesiology, UC Davis School of Medicine, Davis, CA, and the Department of Pharmacology, Georgetown University School of Medicine, Washington, D.C.

Introduction. Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide synthesized by alternative RNA processing of the gene encoding for calcitonin.[1] It is one of the most widely distributed peptide neuromodulators and has many physiological effects. CGRP has been consistently demonstrated to be co-localized and co-released with acetylcholine at the skeletal neuromuscular junction. However, studies of the effects of CGRP on muscle function have produced quite variable results.[2,3] Experiments were designed to evaluate the effects of the pattern of electrical stimulation on the response to CGRP.

Methods. Following institutional animal care committee approval, Sprague-Dawley rats were anesthetized, decapitated, and the isolated, perfused hemi-diaphragm was prepared.[4] The mechanical twitch response to electrical stimulation of the phrenic nerve (0.2Hz, 0.2ms duration, 150% maximal voltage) was recorded. After a period of stabilization, the effects of CGRP on the response to sequential increases in the stimulus duration were then evaluated. The latency, rate of rise, peak response and rate of decay were recorded for each twitch.

Results. CGRP produced a dose-dependent increase in the peak twitch response and in the rate of decay of the contractile force (Tables 1 and 2). No changes were observed in the latency or rate of rise. The effects of CGRP were more pronounced with longer stimulus durations.

Discussion. These data confirm the previously reported potentiation of twitch response by CGRP and demonstrate that discrepancies in published studies may reflect differences in stimulation parameters. In addition, CGRP significantly alters the rate of decay of the twitch response and this effect precedes changes in the peak twitch height. Peptide neurotransmitters may significantly modulate neuromuscular function.

References

1. Prog in Neurobiol 33:335-386, 1989
2. Neurosci Lett 60:227-230, 1985
3. Peptides 9:613-617, 1988
4. J Electrophys Tech 6:40-46, 1978

TABLE 1: **Percent Increase of Contractile Force**
(mean ± SEM)

CGRP	**Stimulus Duration**			
(Moles/l)	0.2*ms*	0.5*ms*	1.0*ms*	1.5*ms*
$1.0*10^{-8}$	-2.2±0.8	-1.9±0.7	3.0±3.7	1.9±2.1
$1.0*10^{-7}$	4.1±3.1	3.9±3.3	18.7±4.0*	14.0±6.0*
$1.8*10^{-6}$	8.7±4.3*	8.3±4.7	25.1±5.2*	20.0±6.4*

TABLE 2: **Average Percent Decrease of 90-10 Decay Time**
(mean ± SEM)

CGRP	**Stimulus Duration**			
(Moles/l)	0.2*ms*	0.5*ms*	1.0*ms*	1.5*ms*
$1.0*10^{-8}$	2.4±1.7	2.0±0.8	2.4±3.1	2.5±3.5
$1.0*10^{-7}$	11.5±5.6	14.6±3.1*	21.5±3.9*	17.4±3.8*
$1.8*10^{-6}$	22.8±7.9*	24.5±5.2*	31.4±5.5*	29.4±5.0*

S77

PHARMACODYNAMIC COMPARISON OF VECURONIUM AND ATRACURIUM

J.E.Fletcher MB, P.S.Sebel MB, S.A.Mick RN
J. Van Duys, MMSC, K. Ryan, MMSC

Department of Anesthesiology
Emory University Medical School, Atlanta GA

Controversy exists concerning the relative histamine releasing and pharmacodynamic effects of atracurium (A) and vecuronium (V). This study compares these drugs at the high and low recommended doses in the data sheets in a double-blind manner.

Forty consenting ASA 1-3 patients age 42 ± 12.3 yr, wt 72 ± 12.9 kg were studied. Patients were randomly allocated into 4 groups: V 0.08mg/kg; V 0.1mg/kg; A 0.4mg/kg; A 0.5mg/kg. Anesthesia was induced with fentanyl 2-5μg/kg and thiopental 4-6mg/kg. A baseline train of four (TOF) (Datex Relaxograph) was obtained. The dose of A or V was then given. BP and pulse were measured pre-induction, pre and post relaxant and post intubation. Blood was drawn for histamine levels at 0, 2, 5 and 10 mins after giving the relaxant. TOF was measured every 20 secs after relaxant. Data are mean ± SD. Statistical analysis was with repeated measures ANOVA and 't' test as appropriate.

There were no differences between groups for demographics, cardiovascular responses or histamine levels. Onset of block was faster in the V groups, reaching statistical significance in the higher doses. (Table) V produced less fade on onset (at T1=50%) than A. During recovery V produced more fade (at T1 recovered to 25%) than A. No cutaneous flushing was seen in any patient.

The recommended dose ranges of V and A for intubation produced equivalent durations of action. However, V has a more rapid speed of onset. We have shown no differences between the drugs in either systemic histamine release, or cardiovascular response when given as in this protocol. If the T1/T4 ratio is a function of pre-synaptic blockade (1), then the differences between A and V suggest different time constants for pre- and post-synaptic receptor effects.

	Onset of block (min)	**T1/T4 ratio at T1=50%** (onset)	**T4(%B-line) at T1=25%** (recovery)
V 0.08mg/kg	4.8±1.7	73±10.5	4.0± 5.5
A 0.4mg/kg	5.8±1.6	60±12.5*	15.0±10.1*
V 0.1mg/kg	3.5±0.8	78±5.8	4.1±6.5
A 0.5mg/kg	5.6±2.2*	63±8.1*	17.1±8.3*

Data are mean ± SD *P<0.05 between A and V

Reference: 1. Miller R (Ed) Anesthesia (1986) 858-859.

S78

PSYCHOMOTOR RECOVERY AFTER DESFLURANE IN OUTPATIENTS

JE Fletcher, MB, PS Sebel, MB, MR Murphy, MD
CA Smith, MD, MP Flister, CRNA, SA Mick, RN

Department of Anesthesiology
Emory University School of Medicine, Atlanta, Georgia

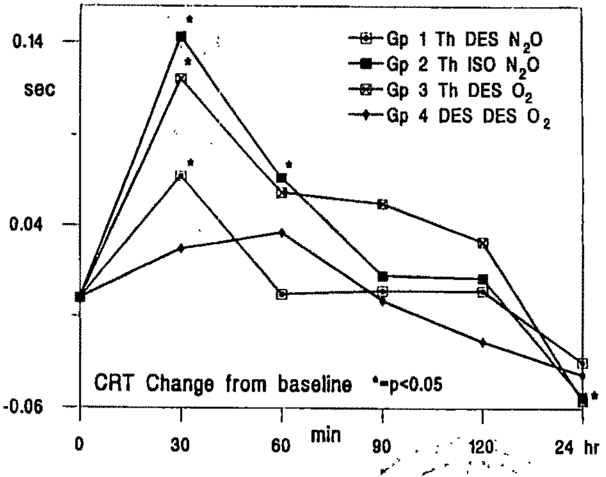
Desflurane (DES) is a new inhalational anesthetic with a blood gas partition coefficient of 0.42. Animal data showed that recovery after DES was faster than other volatile anesthetics (1). This study compares psychomotor recovery in the postoperative period between DES and isoflurane (ISO).

Following Human Investigation Committee approval, 80 consenting unpremedicated outpatients (ASA I-III, age 41±12 yr, weight 77±14 kg) were randomly allocated into four groups: 1. Thiopental (Th)/DES/N_2O/O_2; 2. Th/ISO/N_2O/O_2; 3. Th/DES /O_2; 4. DES inhalational induction/DES/O_2. Succinylcholine was used to facilitate intubation. Anesthesia was maintained with 1.3 MAC DES (no N_2O) or 1 MAC ISO or DES (with N_2O) with normocapnic ventilation. Psychomotor testing, Critical Flicker Fusion Threshold (CFFT) and Choice Reaction Time (CRT), were performed preoperatively, and at 30, 60, 90, 120 minutes, and 24 hours after discontinuation of the anesthetic agent. Data are mean ± SD. Statistical analysis was with t-test.

Patients in groups receiving Th did not differ in time to open eyes. Group 4 (7.9±2.4 min) opened eyes earlier ($p<0.05$) than Group 2 (11.5±4.7 min) and Group 3 (12.1±8.0 min). CRT did not alter in Group 4. Return to baseline performance occurred at 60 min in Groups 1 and 3, and 90 min in Group 2 (see graph). CFFT did not alter in Groups 2 or 4. Return to baseline performance occurred at 90 min for Group 1, and at 30 min for Group 3, who subsequently deteriorated at 60 min. The number of outpatients too sleepy to perform psychomotor tests at 30 min were 1 (Group 1), 2 (Group 2), 7 (Group 3) and 1 (Group 4).

Recovery of CRT performance is faster with DES than ISO. Paradoxically, Group 1 patients (with N_2O) performed better than Group 3 (without N_2O). Addition of Th tends to slow early recovery.

REFERENCE: 1. Eger II EI, Johnson BH: Anesth Analg 1987;66:977-982.



S79

Title: VOLATILE ANESTHETIC EFFECT ON SEROTONIN INDUCED VASOMOTION IN ISOLATED CANINE CEREBRAL ARTERIES

Authors: N Flynn MB BSc FFARCSI, ZJ Bosnjak PhD and JP Kampine MD PhD
Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

Serotonin (5HT) is a naturally occurring amine released by platelets and is a powerful vasoconstrictor of the cerebral arteries. However, some studies have shown that 5HT can also stimulate the release of endothelium-derived relaxing factor (EDRF).[1,2] Following observation of a biphasic action of 5HT on isolated cerebral vessels (i.e. contraction followed by initial relaxation of 30-45% and a slow return to baseline, Fig. 1), we investigated the possible effects of volatile anesthetics on this action.

Following institutional approval, canine middle cerebral arteries (MCA) were removed, carefully divided into 2.5 mm segments and suspended in temperature controlled (37°C) baths containing modified Krebs solution equilibrated with 93.5% O_2 and 6.5% CO_2 to maintain pH at 7.4 and PCO_2 at 35-40 mmHg. In one group of vessels (n=7) the endothelium was removed by gentle scraping of the lumen with the finely shaved wooden pick. The calcium ionophore A23187 (0.1 µM) was used to verify the presence or absence of endothelium since it produces endothelium-dependent relaxation.[3] NG-monomethyl-L-arginine (LnMMA 300 µM) was used in some of the endothelium intact group of vessels (n=6) to inhibit EDRF mediated responses. The EDRF response to A23187 at concentrations greater than 30x the test dose was abolished by LnMMA. The rest of the intact group of vessels (n=8) were constricted in the presence of isoflurane (ISO; 1 mM) or halothane (HAL; 1.2 mM). Data were analyzed by student t-test.

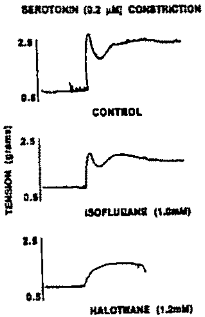


Figure 1

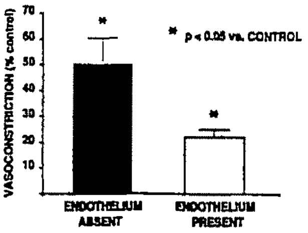


Figure 2

In the endothelium-stripped vessels, 5HT caused a significantly greater constriction than in the endothelium intact vessels (Fig. 2) and the biphasic action was completely abolished. In the endothelium intact vessels, LnMMA also abolished the biphasic action of 5HT. ISO, although it significantly reduced the response to 5HT (70% of control), it did not effect the biphasic action. HAL abolished the biphasic action in 75% of the segments. However, at the concentration of HAL used, there was a significant reduction in the overall 5HT response (52% of control) and the disappearance of the biphasic action may have been due to an overall depressive effect of HAL. This relaxation phase would appear to be EDRF mediated as evidenced by its disappearance with the removal of the endothelium or the addition of LnMMA. However, this EDRF mediated response was unaffected by isoflurane and it is also unlikely that this response is specifically effected by HAL.

References: 1) Nature 305:627,1983; 2) J Pharm Exp Ther 244:1, 1988; 3) Hypertention 4(2):II19,1982.

S80

TITLE: MECHANISM OF THE INHIBITION OF NEUROMUSCULAR TRANSMISSION BY ADENOSINE IN MICE

AUTHORS: FF Foldes MD, I Chaudhry DVM, O Nagano MD, Y Ohta MD, ES Vizi MD
AFFILIATION: Department of Anesthesiology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY 10467

Introduction. Adenosine (ADEN) and 2-chloroadenosine (CADO) inhibit neuromuscular (NM) transmission (1) by decreasing the evoked release of acetylcholine (ACh)(2). Probably because of the high margin of safety of ACh release at NM junction (3), ADEN and CADO only produce NM block when the margin of safety of NM transmission has been reduced by d-tubocurarine (d-Tc) or Mg^{2+}. It was the aim of the present study to elucidate the mechanism of the presynaptic inhibition of ADEN and CADO on NM transmission.

Methods. In experiments, approved by the Institutional Animal Investigation Committee, phrenic nerve-hemidiaphragm preparations of mice were suspended in modified Krebs' solution. After steady state, partial NM block has been established by combinations of ADEN or CADO with d-Tc or Mg^{2+} during indirect stimulation with supramaximal, square wave impulses of 0.2 ms duration at 0.1 Hz, the stimulation rate was progressively increased to 1,2,5 and 50 Hz. The isometric force of contraction of the muscle was quantitated and continuously recorded.

Results. The partial, steady state NM block caused by combinations of ADEN or CADO with d-Tc was intensified by increasing the stimulation rate (table). Increasing the stimulation rate had no effect on the intensity of the partial NM block caused by combinations of ADEN or CADO with Mg^{2+}.

Discussion. It has been reported (4) that the partial, steady state NM block, produced by d-Tc, that inhibits mobilization of ACh from reserve depots (RES) to release sites (REL), or by its combination with compounds with other mechanisms of action is intensified by increasing stimulation rates. In contrast, the intensity of the NM block caused by Mg^{2+} or by its combination with compounds (e.g. neomycin) which only inhibit release is not intensified by increased stimulation rates. Consequently, the finding that the partial NM block caused by the combinations of ADEN or CADO with Mg^{2+} is unaffected by increasing stimulation rates indicates that these compounds do not inhibit mobilization of ACh, but, similarly to Mg^{2+}, inhibit REL.

References.
1. Nature 232:63-64, 1971
2. J Physiol 346:243-256, 1984
3. J Physiol 191:59-90, 1967
4. Anesthesiology 71:218-223, 1989

Compounds	% Block with Stimulation at				Tetanus
	0.1Hz	1 Hz	2 Hz	5 Hz	Maintained
d-Tc + ADEN*	21.0	48.2	65.8	86.1	No
d-Tc + CADO	14.7	29.0	42.9	58.8	No
Mg^{2+} + ADEN	40.6	40.6	42.5	41.9	Yes
Mg^{2+} + CADO	34.6	35.7	36.8	35.8	Yes

*Concentrations (µM); d-Tc 0.8, ADEN 80, CADO 0.8; Mg 3.5 mM.

S81

Title: **REVERSAL OF INTRAOPERATIVE PULSE OXIMETRY FAILURE BY DIGITAL NERVE BLOCK**

Authors: PR Freund MD, TA Bowdle MD PhD, T Neuenfeldt CRNA, K Posner PhD
Affiliation: Department of Anesthesiology, University of Washington, Veterans Affairs Medical Center, Seattle WA

Introduction: We previously reported a prospective study of intraoperative failure of pulse oximetry in 11406 cases from 4 of our university affiliated hospitals[1]. The average failure was 1.12% with a range of 0.56% to 4.24%, the highest failure rate occurring at our Veterans Affairs Medical Center (VAMC). We speculated that the higher failure rate at the VAMC might be attributable to advanced atherosclerotic disease, resulting in a reduction in basal peripheral blood flow, and that any further reduction in blood flow, due to vasoconstriction, could cause the pulse oximeter to fail. To test this hypothesis, we performed a digital nerve block on patients in whom the pulse oximeter failed and assessed the reversibility of the oximetry failure.

Methods: After obtaining approval of human research committees, 648 consecutive patients were enrolled. SaO_2 was recorded every 5 min with vital signs. "Failure" was defined as the inability to obtain SaO_2 for 15 consecutive min. A digital nerve block was then performed with 1% lidocaine (5-10 ml) on the finger to which the oximeter was attached. If a satisfactory pulse oximeter signal returned within 20 min the failure was considered to be "reversed."

Results: The pulse oximeter failed in 19 (2.9%) patients. All were male, with a mean age of 67 years (SD ± 10) and a median ASA status of 3 (range 2-5). They were hemodynamically stable with body temperature >35°C. In 5 patients the anesthesiologist elected not to attempt digital nerve block. 14 patients received a block, resulting in satisfactory pulse oximetry in 10 of 14 (71%), within an average of 10 min (range 5-20 min). There was no significant difference in age or ASA status between successful and unsuccessful blocks.

Discussion: The reversal of 71% of the oximeter failures with a digital nerve block suggests that regional vasoconstriction contributed significantly to oximetry failure in this patient population. Digital nerve block is easily performed and appears to extend the usefulness of pulse oximetry monitoring in geriatric patients.

References:
1. Freund PR, Overand PT, Cooper J et al. A prospective study of intraoperative pulse oximetry failure. J Clin Mon (in press).

S82

TITLE: **ACADEMIC PERFORMANCE AND PERSONALITY TRAITS: INFLUENCE ON PGY-I APPLICANT SELECTION**

AUTHORS: R.P. From, D.O., C.D. Kreiter, M.A., M.A. Albanese, Ph.D., K.S. Pearson, M.D., J.R. Moyers, M.D., M. Gomez, M.D., B.J. Hindman, M.D., D. Murray, M.D., J.H. Tinker, M.D.
AFFILIATION: Department of Anesthesia, University of Iowa, Iowa City, IA 52242

We attempted to determine the relative influence of various academic performance criteria and personality traits on PGY-I resident applicant rank ordering at our institution.

Seven faculty members, on a rotating schedule, interviewed candidates individually for 20 min and then completed a 21-item questionnaire. These faculty ratings were not used for the final ranking session, rather, interviewers used their own notes during a group consensus ranking session.

There were 88 interviews conducted on 10 days. As expected, two distinct dimensions (academic and personality) were confirmed by Principal Component Factor Analysis. The ratings for each item were entered as predictor variables into separate regression equations using rank as the dependent variable. Academic performance accounted for 47% of the variability in candidate ranking while personality traits accounted for 39%. All predictor variables accounted for 67% of the variance. Spearman Correlation between rank order and each predictor variable are shown below.

ACADEMIC PERFORMANCE	Corr.	p value
Dean's letter	0.54	0.0001
Medical school class rank	0.53	0.0001
Other recommendation letters	0.41	0.0001
National board scores	0.39	0.0012
No. basic science honors	0.37	0.0007
Research/publications	0.26	0.0161
PERSONALITY TRAITS		
Intelligent	0.52	0.0001
Educationally self motivated	0.52	0.0001
Commitment to anesthesia career	0.46	0.0001
Aware of own limitations	0.42	0.0001
Good judgment	0.41	0.0003
Flexible/adaptable	0.40	0.0005
Conscientious	0.40	0.0004
Communicative	0.40	0.0002
Appearance	0.39	0.0001
Honest/ethical	0.38	0.0008
Calm under stress	0.33	0.0022
Compassionate	0.32	0.0027
Broad interests	0.32	0.0063
Sense of humor	0.28	0.0122
Rapport	0.26	0.0169

Academic performance and personality traits can be thought of as distinct dimensions with respect to a candidate's qualifications for selection, accounting for 47% and 39% of variability in ranking, respectively. The Dean's letter and medical school class rank are the most influential academic performance variables. The perception by interviewers that a candidate is intelligent and educationally self motivated are the two most influential personality traits.

S83

TITLE: PROTECTIVE EFFECT OF NICARDIPINE AGAINST HYPOXIC INJURY IN THE ISOLATED, PERFUSED RAT LIVER.

AUTHORS: Y. Fujita, M.D., H. Hamada, M.D., K. Kimura, M.D., M. Takaori, M.D.
AFFILIATION: Department of Anesthesiology, Kawasaki Medical School, Kurashiki, Okayama 701-01, Japan

Introduction: It has been suggested that calcium channel blockers provide protection against hypoxic liver injury. As calcium mediates smooth-muscle contraction, the protective effects of calcium channel blockers might be, however, attributed to mechanisms operating at vascular sites. We evaluated effects of nicardipine, a calcium channel blocker, on hypoxic/reoxygenation injury and hepatic circulation using the isolated, perfused rat liver (IPRL).

Materials and Methods: After institutional approval from Animal Experiment Committee, livers from male Sprague-Dawley rats (400-500g) were perfused through catheters inserted into the porta vein and hepatic vein in a recycling system at 37°C. The perfusate consisted of 20-24 % washed bovine erythrocytes in a Krebs-Henseleit solution containing 1.5 g/dl bovine albumin and 100 mg/dl glucose. The perfusate was oxygenated by equilibration with an O_2-CO_2 mixture (95:5). Hypoxia was achieved with a mixture of N_2-CO_2 (95:5). Flow rates were adjusted to obtain a perfusion pressure of 15cm H_2O. The experiment was performed under a constant flow rate. Studies were carried out in two groups; control group (n=5) and nicardipine group (n=5). After a 30 min control perfusion, hypoxia was induced for 120 min, followed by reoxygenation. In the nicardipine group, nicardipine was added to the perfusate reservoir ($2x10^{-6}$M) prior to the hypoxic perfusion. At the end of each stage, perfusion pressure was recorded, and the perfusate was collected for blood gas analysis and lactate dehydrogenase (LDH) determination. Data were analyzed by ANOVA, utilizing a Fischer's LSD test. $P<0.05$ was considered significant.

Results: Though perfusion pressure was similar during control and hypoxic perfusions, a significant increase in perfusion pressure was observed immediately after reoxygenation in the control group (14.5±0.8 to 25.7±3.3 cmH_2O). LDH increased substantially at the end of hypoxic perfusion and during reoxygenation in control group, while nicardipine treatment prevented the increase of LDH(Fig. 1).

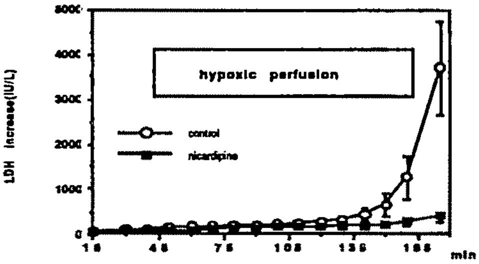


Fig.1

Discussion: The data indicate that reoxygenation aggravates the hepatocellular hypoxic injury and elicits vasospasm of the liver. The vasospasm might be due to calcium-induced vasospasm, because it was prevented by nicardipine pretreatment. We conclude that the protective effects of nicardipine may be related with attenuation of the vasospasm.

S84

TITLE: HALOTHANE AND PROTO-ONCOGENE "c-myc" EXPRESSION

AUTHOR: Y.FUJIWARA M.D.,K.FUJIMAKI M.D. (1)(2),N.MIKE M.D.,K.AZUMA M.D., Y.SHIMADA M.D.(2),T.Naoe M.D.(3)
AFFILIATION: Dept. of Anes., Komaki Municipal Hosp. Komaki, Aichi(1), Dept. of Anes.,School of Med.,Nagoya Univ (2) and Int. Med., Branch Hosp. Nagoya Univ.(3), JAPAN

INTRODUCTION: Recently many kinds of oncogene have been discovered and their functions, such as, oncogenesis, proliferation and metastasis, have been widely reported. Proto-oncogene "c-myc" is the cellular homologue of v-myc isolated from an avian myelomacytosis virus 29. Gene amplification of c-myc resulting in augmented expression has been reported in some human leukemia and carcinoma cell lines as well as in primary tumors. And c-myc expression is important in oncogenesis and tumor cell proliferation. Anesthetics could influence these functions. In this study, we evaluated the effect of halothane on c-myc expression of human leukemia cells, in vitro.

METHODS: Human acute promyelocytic cells from the cell line HL-60, which is one of the most famous cell line with strong "c-myc" expression, were seeded into a dish containing 10% fetal bovine serum and RPMI1640. The dish was placed in an air-tight exposure chamber warmed at 37°C, containing a mixture of gases (20%O2, 5%CO2, 4% halothane and balanced N2). Concentration of each gas was monitored with an infrared gas analyzer (Capnomac, Datex, Finland). After exposure, the leukemia cells were analyzed with "Western Blotting" methods; proteins from homogenized cells were separated with SDS-polyacrylamide electropheresis and electroblotted onto nitrocellulose membrane. The c-myc protein was detected with anti c-myc protein monoclonal antibody and with horse raddish peroxidase methods which were employed for immunostaining.

RESULTS: The density of c-myc protein, an index of c-myc gene expression, did not change in leukemia cells after 3,6,12 and 24 hours of 4% of halothane exposure compared to that of non-exposed cells. The same results were observed in cells exposed to 4% halothane for 24 hours and then incubated in 5%CO2 and air either for 12 or 24 hours.

DISCUSSION: We conclude that halothane does not influence the c-myc oncogene expression. Halothane might not augment oncogenesis and tumor cell proliferation related to "c-myc".

This study was suported by a Grant-in-Aid for the Scientific Research from the Ministry of Education, Science and Culture, JAPAN.

S85

TITLE: CORRELATION BETWEEN ETT SIZE, DISTAL DIGIT DIAMETER AND THE PENLINGTON FORMULAE

AUTHOR: RH Fukuoka MSN, JW Kelly MA,CRNA and CM Franklin MD
AFFILIATION: Kaiser Foundation Hospitals, Los Angeles, CA

Introduction: Both Penlington's formulae and 5th finger distal digit diameter are used to estimate the correct uncuffed endotracheal tube size in the pediatric patient.[1] The accuracy of the digit size has not been formally evaluated.[2] This study compares each method's accuracy in determination of correct pediatric ETT sizes.

Methods: With hospital IRB approval, the A-P distal joint diameter of the left 5th finger was calipered in 53 pediatric patients. The ID of the ETT actually used was determined "correct" if a leak around the tube occured at 15-20 cmH_2O. This ETT was compared to the distal joint diameter and the calculated ETT size as determined by Penlington's formulae: children <6.5 years,ID = (years old/3) + 3.5 children >6.5 years,ID= (years old/4) + 4.5.

Results: The correlation between uncuffed ETT size and distal joint diameter(Figure 1) or with the calculated ETT size Figure 2) were significant (r=.77 and .09 respectively, p=.01). The distal joint diameter was consistently greater than ETT overall diameter (mean = 2.2 mm). Penlington's formulae accurately estimated "correct" ETT size 49% of the time. There was a tendency for the calculated tube to be smaller in diameter than the "correct" ETT size by 0.5 cm.

Discussion: Penlington's ETT size formulae were significantly more accurate in predicting the correct tube size than was the method of using the child's little finger. This accuracy is most likely due to the statistical deviation of the formulae.[3] It should be appreciated that "correct" ETT external diameter will likely be overestimated an average of 2.2 mm when utilizing digit measurement.

References: [1]Anesthesia p.1176, 1986. [2]Pediatric Anesthes. p.463, 1989. [3]British J Anaesth 29:494, 1974.

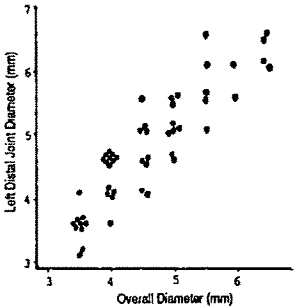


Figure 1
Distal joint diameter (mm) versus overall diameter (mm) of uncuffed endotracheal tube

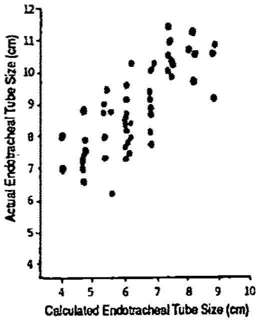


Figure 2
Actual endotracheal tube used (cm) versus calculated endotracheal size (cm)

S86

Title: RESIDENCY PROGRAM CRITERIA FOR COMPLETION OF CLINICAL COMPETENCE REPORTS

Authors: C. Furgerson, M.D. and A. Barnes, M.D.

Affiliation: The Cleveland Clinic Foundation

The American Board of Anesthesiology (ABA) requires residency programs to complete Clinical Competence (CC) reports rating residents Satisfactory/Unsatisfactory (SAT/UNSAT) overall and in 4 individual categories: knowledge, judgement, clinical and character skills.

We surveyed 129 accredited residency programs asking what evaluation tools they use to rate residents' performance; whether they use ABA intraining examination (ITE) scores; had they ever rated a resident UNSAT, and what led to that decision.

49% of programs responded; few (17.9%) required a minimum (5-40%) ITE score; less (12.3%) offered pass/fail departmental written examination(s). Most programs (90%) had rated a resident's overall UNSAT performance during training; 31% had ever rated a resident UNSAT at the end of residency. Reasons for UNSAT rating were (in decreasing frequency): character skills, staff evaluations, CC committee concensus, inadequate knowledge/clinical performance, drug abuse.

An UNSAT rating is most likely to result from poor character skills and overall staff assessment of resident performance. Clinical performance is also significantly influenced by non-cognitive factors such as attitude (1). The findings of this survey suggest that character skills may be the determining factor in the ratings of overall resident performance. Further analysis will help clarify the evaluation tools used for each CC category.

Reference
J. Keck, Ph.D., et al Efficacy of cognitive/noncognitive measures In Predicting Resident-Physician Performance. J Med Educ 54:759-65, 1979.

S87

Title: DOES ISOFLURANE ANESTHESIA AFFECT GROWTH OF METHYLCHOLANTHRENE-INDUCED RAT SARCOMA?

Authors: J.A. Gatell, M.D., M.E. Burt, M.D., Ph.D., R.F. Bedford, M.D., R. Reinsel, Ph.D.
Affiliation: Dept of Anesthesiology & Critical Care Medicine and Surgery, Memorial Sloan-Kettering Cancer Center, NY, NY 10021

Introduction: Cancer cells are often liberated into the circulation at the time of oncologic surgery. To determine whether isoflurane(Iso) anesthesia affects cancer growth, recurrence or reimplantation, we studied the development of methylcholanthrene (MC)-induced sarcomas in Fischer 344 (F344) rats receiving multiple Iso anesthetics before primary tumor excision. This tumor model produces palpable tumors in 10-12 days, with local invasion, rare metastasis and death in all rats within 5 weeks.

Method: Day 0, Institutional Animal Care and Use Committee approved, 48 F344 male rats, 200-232 gms, were inoculated subcutaneously in the right flank with approximately 10^6 viable MC-induced F344 rat tumor cells diluted in 0.25 ml normal saline. The rats were then randomized into 2 groups. Group I consisted of 30 rats which received Iso, 1.4% in O_2(Datex gas analyzer), for 60 min according to the following schedule: 1/3 received Iso on day 7 and underwent tumor excision on day 14; 1/3 received Iso on days 7 and 14 and underwent tumor excision on day 21; 1/3 received Iso on days 7, 14 and 21 and underwent tumor excision on day 28. Group II consisted of 18 rats that did not receive Iso. 1/3 underwent tumor excision respectively on days 14, 21 and 28 after tumor implantation. After tumor excision, all rats received reimplanted tumor in the opposite flank with 1/10 dose. Rats were examined daily for weight and largest diameter of tumor. Students t-test was used to compare the groups with regard to rat weight, tumor weight and largest tumor diameter. $P<.05$ was regarded as significant.

Results: Comparing groups I and II at days 14, 21 and 28, there was no difference with regard to either the weight gain of the rats or the size and weight of their primary, recurrent and reimplanted tumors.

Conclusions: In this tumor model, it does not appear that either single or multiple exposures to Iso affect the growth of the syngeneic MC-induced F344 sarcoma in vivo. Contrary to the results of other studies using other anesthetics, we could find no evidence that Iso acts to facilitate tumor growth.

References: 1. Schatten WE, Kramer WM: An experimental study of postoperative tumor metastases. II. Cancer 2:460-462, 1958. 2. Weese JL, Ottery FD, Emoto SE: Do operations facilitate tumor growth? An experimental model in rats. Surgery 100:273-277, 1986.

S88

TITLE: COMPARATIVE EFFECTS OF DESFLURANE AND ISOFLURANE ON NEUROMUSCULAR FUNCTION

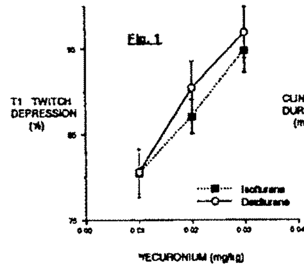
AUTHORS: A. F. Ghouri, P. F. White, Ph.D., M.D.
AFFILIATION: Department of Anesthesiology, Washington University, St. Louis, MO 63110

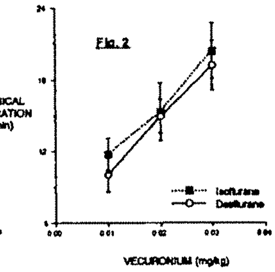
Desflurane (I-653) is a methyl ethyl ether which differs from isoflurane by the substitution of a fluorine for a chlorine at the alpha-ethyl position. Since isoflurane enhances the muscle relaxant effects of nondepolarizing drugs, we designed a study to compare the effects of equipotent concentrations of desflurane and isoflurane on vecuronium-induced neuromuscular blockade.

40 healthy, consenting, unpremedicated adult patients undergoing elective surgical procedures were randomly assigned to one of two anesthetic treatment groups according to an IRB-approved protocol. Following a standardized induction sequence consisting of fentanyl, 3 ug/kg, thiopental, 4 mg/kg, and succinylcholine, 1.5 mg/kg iv, patients received either isoflurane 0.6% (0.5 MAC) or desflurane 3.0% (0.5 MAC) with nitrous oxide 60% in oxygen for maintenance of anesthesia. Neuromuscular function was monitored using a Relaxograph NMT monitor with the stimulating and ground electrodes placed over the ulnar nerve and the recording electrodes positioned over the dorsal interosseus muscle and on the index finger. Baseline measurements of neuromuscular blockade were obtained before and after succinylcholine administration. When the twitch response returned to within 5% of the pre-succinylcholine baseline, a bolus dose of vecuronium 0.01, 0.02, or 0.03 mg/kg iv, was administered at a constant end-tidal concentration of either isoflurane, 0.6%, or desflurane, 3.0% with 60% nitrous oxide. The maximum blockade (percentage of T_1 depression), clinical duration (time from injection to 25% recovery of T_1), and the T_1 relaxation index (time from 25% to 75% recovery of T_1) were calculated. Statistical analysis was performed with Fastat using ANOVA and Student's t-test, with $p<0.05$ considered statistically significant (mean values ± S.E.M. are reported).

The maximal degree of neuromuscular blockade (fig. 1), as well as the clinical duration of relaxation (fig. 2), following vecuronium 0.01, 0.02 or 0.03 mg/kg iv were similar at equipotent concentrations of the two volatile agents. Furthermore, the vecuronium T_1 relaxation indices did not differ between the two volatile anesthetic treatment groups (not shown).

In conclusion, vecuronium-induced neuromuscular blockade is similar when administered in the presence of equipotent (0.5 MAC) concentrations of desflurane and isoflurane.





S89

TITLE: EFFECT OF DESFLURANE ON VECURONIUM-INDUCED NEUROMUSCULAR BLOCKADE

AUTHORS: A. F. Ghouri, P. F. White, Ph.D., M.D.
AFFILIATION: Department of Anesthesiology, Washington University, St. Louis, MO 63110

Desflurane, a rapid and short-acting derivative of isoflurane, will likely be used for maintenance of general anesthesia with intermediate-acting muscle relaxants. Since volatile anesthetics are known to potentiate the neuromuscular blocking properties of non-depolarizing relaxants, we studied the interaction between desflurane and vecuronium during general anesthesia.

54 healthy consenting adult patients undergoing elective surgical procedures were randomly assigned to one of three desflurane treatment groups according to an IRB-approved protocol. After a standardized induction sequence, patients received one of three desflurane concentrations: 1.5% (0.25 MAC), 3.0% (0.5 MAC), or 6.0% (1.0 MAC) in combination with nitrous oxide 60% in oxygen. Baseline twitch measurements were obtained after induction of anesthesia with thiopental, 4mg/kg iv, using a Relaxograph^R NMT device with the stimulating and ground electrodes placed over the ulnar nerve and the receiving electrodes placed over the dorsal interosseous muscle and on the index finger. Succinylcholine, 1.5 mg/kg iv, was administered to facilitate tracheal intubation. When the twitch height returned to within 5% of the baseline value, vecuronium 0.01, 0.02, or 0.03 mg/kg iv, was administered in the presence of a stable end-tidal desflurane concentration of 1.5, 3.0, or 6.0% (with 60% N_2O). The maximum blockade (% T_1 depression), clinical duration of blockade (time from injection to 25% recovery of T_1), and T_1 relaxation index (time from 25% to 75% recovery of T_1) were calculated. Data analysis was performed using ANOVA and Student's t-test, with $p<0.05$ considered statistically significant.

The neuromuscular relaxant properties of vecuronium, 0.01-0.03 mg/kg, in the presence of desflurane, 1.5% to 6%, are summarized below (means ± S.D.). The percent of T_1 twitch depression and duration of blockade increases as a function of the vecuronium dose. However, there was no evidence of desflurane-induced potentiation over the concentration range we studied.

In conclusion, these data suggest that desflurane concentrations from 1.5% to 6% produce minimal changes in vecuronium-induced neuromuscular blockade.

	T_1 depress.	Duration	T_1 index
Vecur. = 0.01 mg/kg	(%)	(min.)	(min.)
1.5% (0.25 MAC)	82.2± 9.6	10.4± 2.5	10.2± 2.4
3.0% (0.50 MAC)	80.7± 9.1	10.0± 4.9	11.9± 3.9
6.0% (1.0 MAC)	80.4± 8.9	9.1± 4.3	10.4± 3.3
Vecur. = 0.02 mg/kg			
1.5% (0.25 MAC)	89.2± 9.5	14.8± 4.6	11.2± 3.4
3.0% (0.50 MAC)	90.5±10.8	14.9± 5.1	9.6± 2.9
6.0% (1.0 MAC)	91.5± 8.7	15.8± 7.4	9.8± 4.7
Vecur. = 0.03 mg/kg			
1.5% (0.25 MAC)	97.8±11.1	19.5± 7.1	10.2± 7.1
3.0% (0.50 MAC)	96.9±10.5	19.2± 7.2	11.2± 7.6
6.0% (1.0 MAC)	98.1± 9.9	19.4± 6.3	13.4± 4.0

S90

Title PROFOUND NEUROMUSCULAR BLOCKADE DOES NOT REDUCE THE HEMODYNAMIC RESPONSE TO TRACHEAL INTUBATION IN MAN

Authors N. Gibbs, MBBS, B. Harrison, MBBS.

Affiliation Dept of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands, WA, 6009, Australia.

Introduction Although neuromuscular blockade is widely used to facilitate tracheal intubation, it is not known whether the extent of neuromuscular blockade (NMB) affects the hemodynamic response to tracheal intubation. The aim of the current study was to examine the effect of two different levels of non-depolarizing NMB on the heart rate (HR) and mean arterial pressure (MAP) responses to tracheal intubation in humans.

Methods After Human Rights Committee approval and written informed consent, 32 adult ASA I patients scheduled for elective surgery were studied. The patients were randomized to receive either vecuronium (VEC) 0.05$mg.kg^{-1}$ iv (1xED_{95}, group 1) or VEC 0.125$mg.kg^{-1}$ iv (2.5xED_{95}, group 2) for tracheal intubation. In both groups anesthetic induction was achieved with midazolam 0.02$mg.kg^{-1}$ iv, fentanyl 2$\mu g.kg^{-1}$ iv, and pentothal 5$mg.kg^{-1}$ iv. The VEC was given immediately after induction. The patient's lungs were ventilated with 66% N_2O in O_2 for 3min before intubation. No other drugs were used until 2 min post-intubation. Intubation was performed by an anesthesiologist blinded to the patient's group and was completed within 30s. NMB was assessed by measuring the evoked electromyogram (EMG) of the abductor digiti minimi to transcutaneous stimulation of the ulnar nerve. HR and MAP were measured every 20s using a Dinamap 1846SX in "stat" mode. Intubating conditions were scored using criteria previously described by Fahey *et al* (0=excellent, 3=unsatisfactory)[1]. The maximum changes (Δ) in HR and MAP in response to tracheal intubation, and the evoked EMG at the time of intubation, were compared between the two groups using two-tailed *t* tests. The intubation scores were compared using a Mann-Whitney *U* test. *P* values <0.05 were considered significant.

Results There were no significant differences in the ΔHR or ΔMAP responses between the groups (table). The evoked EMG at the time of intubation in group 1 was significantly greater than in group 2 ($P<0.01$), and the intubation conditions in group 2 were significantly better than in group 1 ($P<0.01$).

Table The Effect of NMB on Intubating Conditions and on HR and MAP Responses to Tracheal Intubation

Group	EMG at Intubation (%control)	ΔHR (beats/min)	ΔMAP (mmHg)	Intubation Score[1]
Group 1	46.7±4.5	20.3±2.1	34.0±3.7	1.3±0.1
Group 2	5.4±1.7*	22.8±2.6	35.2±3.0	0±0*

Values are mean±SEM. *Indicates $P<0.05$.

Discussion The results demonstrate that increasing the level of non-depolarizing NMB improves intubating conditions but does not reduce the hemodynamic response to intubation. The results support the concept that NMB is only an adjunct to anesthesia and that NMB *per se* does not increase anesthetic depth.

Reference 1. Anesthesiology 1981;55:6-11.

S91

TITLE: THE COMPARISON OF THE USE OF THREE NARCOTICS DURING AWAKE CRANIOTOMY

AUTHORS: EA Gignac, MD, PH Manninen, MD, AW Gelb, MB,ChB
AFFILIATION: Dept. of Anaesthesia, University Hospital,
London, Ontario, Canada N6A 5A5

Introduction: Awake craniotomy is performed on patients with pathologic lesions located near eloquent brain areas. Local anesthesia with neurolept analgesia using a short-acting narcotic such as fentanyl is frequently used. This allows for patient cooperation during localization of the seizure focus and adjacent cortical areas. The purpose of this study was to compare the effectiveness of sufentanil (S) and alfentanil (A) to fentanyl (F) in providing adequate analgesia with minimal side effects.

Method: After ethics approval, informed consent was obtained from 30 patients presenting for awake craniotomy for seizures. Each patient was randomly assigned to receive one of F, S or A in a double-blinded manner. Patients were monitored with an electrocardiogram, automated blood pressure cuff, pulse oximetry and end tidal CO_2. Just prior to surgery, droperidol 0.014 mg/kg, dimenhydrinate 0.25 mg/kg IV, and a narcotic bolus (F- 0.75 µg/kg; S- 0.075 µg/kg; A- 7.5 µg/kg) were administered followed by an infusion (F- 0.01 µg/kg/min; S- 0.0015 µg/kg/min; A- 0.5 µg/kg/min). Additional doses of dimenhydrinate or droperidol for nausea, emesis or for sedation were administered at the anesthetist's discretion, as well as incremental (1/2 of bolus) doses of the study narcotic for pain. All complications were documented. Statistical analysis was performed using analysis of variance and chi square test. $P<0.05$ was considered significant.

Results: There were no statistically significant differences between groups for patient characteristics, the incidence of desaturation (O_2 Sat < 92%), hypercarbia ($ETCO_2$ > 47), nausea, vomiting, seizures, level of sedation, or the patient's ability to cooperate (Table). Two patients in the F group required general anesthesia for completion of the procedure due to inability to cooperate. No significant differences were found in droperidol, dimenhydrinate or recovery room analgesia requirements between groups. Surgeon satisfaction, electroencephalographic recording and stimulation testing were satisfactory for all patients. Allowing for potency differences, the amount of A used was three times that of F which is consistent with A's shorter duration of action. Since the effectiveness of the three drugs was similar, this makes A the more expensive drug.

	Fentanyl	Sufentanil	Alfentanil
Age (years)	37 ± 12	30 ± 11	31 ± 10
Weight (kg)	72 ± 10	78 ± 13	65 ± 17
Sex (M:F)	4:6	7:3	5:5
Length (hours)	5.4 ± 1.7	5.1 ± 1.0	5.5 ± 1.4
Narcotic Requirement µg/kg/hr	.88 ± .32	.12 ± .05	28.4 ± 7.1
Seizures (number of patients)	1	3	1
Nausea & vomiting (number of patients)	4	2	5

Values are mean ± SD

Discussion: Previous reports have retrospectively analyzed the anesthetic management of awake craniotomies.[1,2] Alfentanil in larger doses has also been successfully used.[3] In this prospective study, we found that F, S and A given as a bolus followed by an infusion are equally effective in providing patient comfort and good surgical conditions without any difference in the incidence of side effects.

References:

1. Can J Anaesth 1988, 35:338-44.
2. Int Anesth Clin. Varkey (Ed.) Fall 1986, 24:157-173.
3. Anesth Analg 1989; 68:57-60.

S92

Title: EPIDURAL VERSUS INTRAVENOUS FENTANYL DURING CESAREAN SECTION

Authors: GJ Grant MD, I Ho BS, E Winter MD, S Ramanathan MD, H Turndorf MD
Affiliation: Department of Anesthesiology, New York University Medical Center, New York, NY 10016

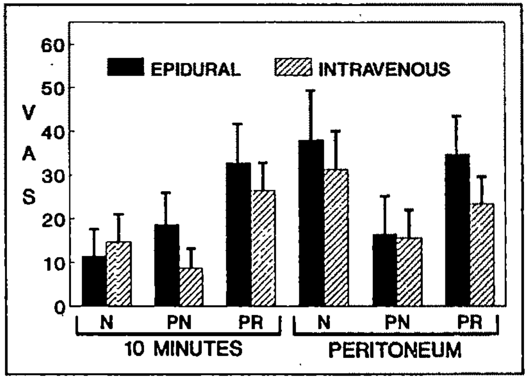
Introduction: Studies have shown that epidural narcotics improve the quality of anesthesia during cesarean section (C/S) under lumbar epidural anesthesia (LEA)[1-5]. However, these studies did not include parenteral narcotic controls. This study compares in a randomized double-blind manner these two routes of fentanyl administration.

Methods: The study was approved by the institutional review board and informed consent was obtained. LEA with 2% lidocaine with 1:200,000 epinephrine to a T4-T2 level was given for elective C/S. After delivery, patients received fentanyl 100 µg epidural (n=12) or i.v. (n=16). All patients had their uterus exteriorized during closure. Patients used a 100 mm visual analog scale (VAS) to grade nausea, pain and pressure 10 minutes after fentanyl dose, during peritoneal closure and after fascial closure. A blinded anesthesiologist graded their overall comfort on a VAS. Plasma fentanyl levels were measured using a radioimmunoassay (sensitivity 0.1 ng) at 5, 10, 15, 30, 60, 120, 180 and 240 min (n=5 per route). The frequency of patients complaining of no side effects or severe discomfort (>66 on VAS) was compared using X^2 analysis. VAS scores were analyzed using a Mann-Whitney-U test at $p<0.05$.

Results: There were no differences between routes with regard to maternal vital statistics, total lidocaine dose, and level of anesthesia. VAS scores for nausea, pain or pressure did not differ at any interval. The frequency of no side-effects or severe side-effects did not differ between the two routes. All patients had detectable fentanyl levels after i.v. administration. None had detectable levels after epidural administration.

Discussion: We conclude that there is no difference between epidural and i.v. fentanyl with regard to patient comfort during C/S under lidocaine epidural anesthesia. The higher plasma fentanyl levels following i.v. fentanyl imply a systemic effect whereas the negligible plasma levels after epidural fentanyl suggest a spinal mechanism.

References: 1.Anesthesiology 1985;63:694-698. 2.Anesthesiology 1986;65:331-334. 3.Anesthesiology 1988;68:938-943. 4.Anaesth Intens Care1989;17:157-165. 5.Anaesth Intens Care 1990;18:22-30.



Visual analog scores (± S.E.) at 10 minutes after fentanyl dose and during peritoneal closure. N=nausea, PN=pain, PR=pressure. No significant differences between routes.

S93

Title: CONTINUOUS INFUSIONS OF ALFENTANIL IN INFANTS UNDER ONE YEAR OF AGE UNDERGOING INGUINAL HERNIORRHAPHY

Authors: B. Gronert, M.D., P.J. Davis, M.D., and D. R. Cook, M.D.

Affiliation: Department of Anesthesiology, Children's Hospital of Pittsburgh, Pittsburgh, PA 15213-2583

Introduction: Because of respiratory depression, the use of narcotics in anesthesia for infants is controversial. The purpose of this study was to evaluate the safety and efficacy of continuous alfentanil infusion in infants less than one year of age undergoing outpatient inguinal herniorrhaphy.

Methods: After our institution's IRB approval and written, informed consent from a parent, 34 ASA I-II patients scheduled for bilateral inguinal herniorrhaphies, were randomized into 2 groups. Both groups underwent inhalation induction via mask with halothane/N_2O 70%/O_2 30%. After the induction of anesthesia, atracurium 0.5 mg/kg and atropine 0.1 mg (total) were administered intravenously to prevent chest wall rigidity, facilitate endotracheal intubation, and prevent bradycarida, respectively. In group I (N=15) halothane was discontinued and alfentanil, 100 mg/kg, was administered, and then an infusion of 2 µg/kg/min; supplemental alfentanil boluses (10 mg/kg) were given in response to hemodynamic changes greater than 20% above baseline. In group II (N=18) halothane was maintained and adjusted to the anesthetic needs.

The following parameters were recorded: heart rate and blood pressure during induction and incision, duration of anesthesia and surgery; times to extubation, wakefulness, and first oral intake; oxygen saturation (SpO_2) and respiratory rate (RR) on admission and discharge from recovery room, duration of recovery room and outpatient unit stay; and postoperative vomiting and analgesia requirements. All data were analyzed with analysis of variance, unpaired t-test, Chi-square with Yates correction; statistical significance was considered for $p < 0.05$.

Results: There were no differences between the groups with regard to age, weight, intraoperative hemodynamic changes, recovery room SpO_2 and RR, postoperative vomiting, and pain medication. Although times to extubation were not different between the two groups, group I took significantly longer (15 minutes) to be awake post-extubation than group II. However, the groups were not significantly different in the times to first oral intake and discharge from the outpatient unit.

Discussion: Intravenous anesthesia with alfentanil is safe and effective. The initial bolus and infusion was well-tolerated and maintained better hemodynamic stability than with a single bolus (1). No patients developed apnea or respiratory depression postoperatively. Group I patients were more sedated postoperatively, which tended to delay their first oral intake, but this was not statistically significant.

Reference: 1. Anesth Analg 70:S343, 1990.

Table 1. (mean ± SD)

Group	Postop Meds	Age (wk)	Wt (kg)	Extubation (min)	Awake (min)	Hospitalization (min)	1st Drink (min)
I	2/15	18.1 (±2.9)	6.6 (±.39)	7.9 (±.93)	22.4* (±4.8)	138.7 (±14.3)	142.2 (±17)
II	8/18	23.4 (±3.2)	7.2 (±.46)	6.7 (±.74)	3.5 (±1.7)	127.2 (±11.2)	97.1 (±17)

* $p < .05$ different from group II.

Supported by Janssen Pharmaceutica.

S94

TITLE: PHARMACOKINETICS OF DROPERIDOL IN CHILDREN

AUTHORS: Z. Grunwald, M.D., H. Schieren, Ph.D., and M. Torjman, M.Ed.

AFFILIATION: Department of Anesthesiology,
Jefferson Medical College,
Thomas Jefferson University,
Philadelphia, Pennsylvania 19107

Introduction: Droperidol is a butyrophenone which has been used effectively to decrease the incidence of vomiting following strabimus and tonsillectomy surgery in children.[1,2] At present, however, there is no information available regarding the pharmacokinetics of droperidol in the pediatric population. The purpose of our study was to evaluate the pharmacokinetics of droperidol in children with a clinically relevant dose.

Methods: After obtaining IRB approval and parental consent, we studied 12 ASA PS I and II children aged 7.5±2.5 years scheduled for tonsillectomy and adenoidectomy. Premedication was not used here. The anesthetic technique consisted of: inhalation induction, using halothane and nitrous oxide in oxygen; muscle relaxation with vecuronium bromide; and intravenous morphine sulfate (0.1 mg/kg). Each patient received intravenous droperidol at 50 mcg/kg.

Venous samples were obtained from an indwelling catheter before the administration of the drug and at 1, 2, 4, 6, 10, 20, 40, 60, 120, 180, 240, 300, 360 minutes postadministration. Droperidol plasma concentrations were measured with radioimmunoassay.[3] The pharmacokinetics were evaluated by model-independent methods to obtain values for plasma clearance (Cl), volume of distribution (Vd_{ss}), half-life ($t_{1/2}$), and mean residence time (MRT).[4]

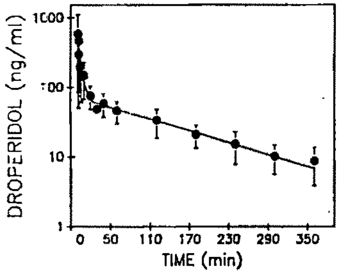
Results: The pharmacokinetic parameters for droperidol are presented in the Table. The plasma concentration of droperidol as a function of time is shown in the Figure.

Discussion: The Cl and Vd_{ss} values are apparently lower than those reported for adult populations, and the $t_{1/2}$ and MRT are in accord with values reported for adults.[3,5] This finding is consistent with the similar clinical effect of droperidol observed in both pediatric and adult cases.

Droperidol Pharmacokinetics (Mean±S.D.)

Table	MRT (min)	Cl (ml/kg/min)	Vd_{ss} (L/kg)	$t_{1/2}$ (min)
	127±28.7	4.7±2.3	0.58±0.29	102±26.4

Figure



References:
[1] Anesthesiology 59: 579-583, 1983.
[2] Anesth Analg 70: S138, 1990.
[3] Anesthesiology 64: 486-489, 1985.
[4] Pharmacokinetics Marcel Dekker, 433-444, 1982.
[5] Br J Anaesth 61: 297-301, 1988.

S95

TITLE: RADIANT HEAT REDUCES REQUIREMENT FOR VASODILATOR DRUGS AFTER CARDIOPULMONARY BYPASS

AUTHORS: R.H. Gulden, MSIII, C.W. Whitten, MD, T. Latson, MD, J.M. Lipton, PhD, P.Cochran, MD, J. Elmore, MD

AFFILIATION: Department of Anesthesiology and Division of Thoracic/Cardiovascular Surgery, University of Texas Southwestern Medical Center, Dallas, Texas 75235

INTRODUCTION: Shivering and hypothermia after cardiopulmonary bypass (CPB) can place a significant stress on the cardiovascular system. The purpose of the present research was to determine the effectiveness of radiant heat in attenuation of this cardiovascular stress.

METHODS: After institutional approval and informed consent, 20 patients were randomly assigned to two groups: group 1 [n=8 (G1)] received radiant heat[1] applied to the blush region for four hours after arrival in the intensive care unit (750 watts; 39° skin target temperature) and group 2 [n=12 (G2)] received conventional treatment (warm blankets). The following parameters were monitored for 4 hours: hemodynamic profile, pulmonary artery temperature, hemoglobin, arterial blood gas, and dosage of vasoactive drugs. The mean blood pressure was controlled via infusion of nitroglycerine and/or nitroprusside to maintain the systolic blood pressure between 100 and 130 mmHg.

RESULTS: No differences were noted between G1 and G2 in the length of rewarming during CPB, the hypothermic target temperature for CPB, time of CPB, total operating room time, body surface area, or mean blood pressure. One patient in G1 shivered (onset at arrival, duration 55"), whereas four patients in G2 shivered (mean onset 88" after arrival in the ICU; mean duration 90"). The SVO2 remained unchanged in G1 whereas it decreased significantly during the study interval in G2 ($p < .05$, Student's t-test; Fig. 1). Figure 2 illustrates that the average requirement for vasodilator drugs was decreased in G1. This difference became statistically significant ($p < .05$, one-tail t test) at 135" following arrival in the ICU, and remained significant throughout the remainder of the study interval. Seven of 12 G2 patients required sodium nitroprusside (SNP) while only two required SNP in G1, one of which had SNP withdrawn after 60".

Figure 1

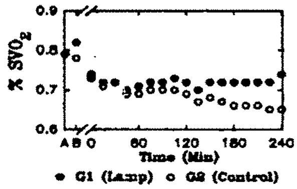
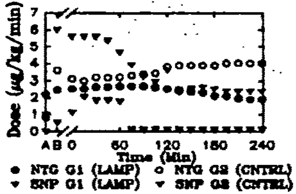


Figure 2



A=End of Cardiopulmonary Bypass B=Departure from OR
0 Minutes=Time of arrival in ICU

DISCUSSION: The results indicate that radiant heat after CPB attenuates the decrease in SVO2 and reduces the requirement for vasodilators. The decreased requirement for vasodilators may stem not only from the direct effects of radiant heat (vaso- and venodilation) but also from a reduction of the shivering and vasoconstriction under nervous control. Although not significant in this study, those patients warmed with radiant heat tended to have a higher rate of rewarming when compared with those treated with warm blankets. The higher SVO2 level and the decreased vasodilator requirement in the group receiving radiant heat indicates that this therapy effectively attenuates the cardiovascular stress associated with shivering and/or hypothermia, and supports the use of radiant heat in the post-CPB patient.

REFERENCES:

1. Lipton JM, et al: Anesth Analg 70:S243, 1990.

S96

TITLE: CENTRAL α_1 ADRENOCEPTOR STIMULATION FUNCTIONALLY ANTAGONIZES THE HYPNOTIC RESPONSE TO DEXMEDETOMIDINE, AN α_2 AGONIST

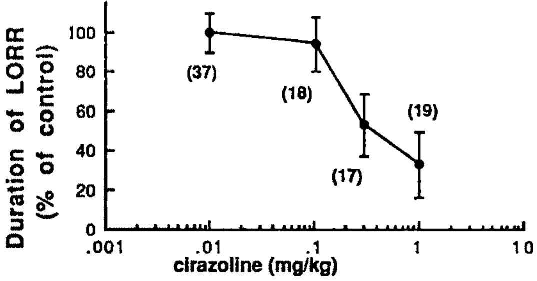
AUTHORS: T-Z. GUO M.D., J. TINKLENBERG B.S.
R. OLIKER, M. MAZE M.B.
AFFILIATION: DEPARTMENT OF ANESTHESIA, STANFORD UNIVERSITY, & VAMC, PALO ALTO, CA94304

INTRODUCTION: The hypnotic dose-response to the systemically-administered α_2 adrenergic agonist, dexmedetomidine (dex), is biphasic[1]. Reversal of the hypnotic response, which was noted at the higher doses of dex, could be blocked by pretreatment with prazosin, an α_1 antagonist. Therefore, we wondered whether activation of central α_1 adrenoceptors functionally antagonizes the hypnotic response to stimulation with an α_2 agonist.

METHODS: Following approval from the Animal Care and Use Committee, rats were anesthetized with dex, 0.25 mg.kg^{-1}, i.p. a dose which consistently produces loss of righting reflex (LORR) for a period of from 3 - 4 h. Rats were pretreated (10 min earlier) with the CNS-permeant α_1 agonist cirazoline, 0.01-1 mg.kg^{-1} i.p., or the CNS-impermeant phenylephrine, 0.3-3.0 mg.kg^{-1} i.p., which are comparable hemodynamic doses, and the duration of LORR was measured. To determine whether the hypnotic-attenuating effects of cirazoline were produced by a central or peripheral α_1 adrenoceptor, duration of LORR was measured in further groups of rats which were additionally pretreated with either prazosin, or doxazosin, CNS-permeant and CNS-impermeant α_1 antagonists, respectively, before combinations of cirazoline and dex. Further cohorts of rats were chronically implanted with cannulae into the lateral ventricle for intracerebroventricular (icv) drug administration. Either cirazoline (0.1 mg.kg^{-1}) or dex (30 µg.kg^{-1}) was administered icv (i.e. at doses that would not produce any behavioral effect if given systemically), together with the opposite drug i.p. and the duration of LORR was measured. Data were analyzed by ANOVA and t-test and significance established at a $p < 0.05$.

RESULTS: Cirazoline, dose-dependently, attenuates the hypnotic response to dex (Fig 1)while phenylephrine, the CNS-impermeant α_1 agonist is inactive. Cirazoline's hypnotic attenuating effect is completely blocked by prazosin but only partially by the CNS-impermeant α_1 antagonist doxazosin. ICV-administered cirazoline significantly attenuated the hypnotic response to i.p. dex and i.p.-administered cirazoline attenuated the hypnotic response to icv dex.

Effect of cirazoline on duration of LORR produced by dexmedetomidine, 0.25 mg/kg, in rats (n)



DISCUSSION AND CONCLUSION: Stimulation of central α_1 adrenoceptors functionally antagonizes an α_2 adrenoceptor-mediated hypnotic response. This is an example of postreceptor cross-talk. Thus, an α_2 agonist needs to be superselective (>1000:1) for the α_2 *vs* the α_1 adrenoceptor to be maximally efficacious perioperatively.

REFERENCE: 1. Anesthesiology 71:75-79, 1989

ACKNOWLEDGEMENTS: NIH(GM30232),VA,&,FarmosRes. Group.

S97

Title: MUSCARINIC RECEPTOR SUBTYPE SELECTIVITY OF TROPACOCAINE DERIVATIVES IN THE RAT

Authors: L. Gyermek. N. Nguyen, and C. Lee
Affiliation: Dept. of Anesthesiology, Harbor-UCLA Medical Center, Torrance, CA 90509

Based on our observations with bisquaternary derivatives of atropine (1) we decided to explore structure-activity relationships of different cholinergic receptor types and subtypes by using derivatives of tropacocaine. Methods: Male rats (300-450g) were anesthetized (Nembutal 40mg/kg ip) with approval of the Animal Investigation Committee. After tracheostomy artificial ventilation with O_2 was given and normocarbia, normothermia and hydration was maintained. Transduced arterial BP(common carotid a), heart rate (ECG) and neuromuscular transmission (evoked EMG responses to supramaximal "train-of-four" stimuli each 12 sec. to the sciatic n.) were monitored. Polymethylene (C_{3-10}) bis N, N' quaternary ammonium halides(Br) of tropacocaine, dissolved in normal saline, were given iv. Pharmacologic blockade of 4 different responses, related to muscarinic (M_{1-3}) and to neuromuscular(Nnm) receptors, were studied on 4 groups of rats: Group I (M_1 receptor block): Under anesthesia the spinal cord was transected at the atlanto-occipital level. On the spinal preparation the M_1 receptor stimulant action of 50-200µg/kg McN343 (vasopressor responses) were antagonized. Group II (M_2 receptor block): The right vagus nerve was stimulated at 2 min. intervals with trains of impulses (0.2 ms., 10-15 Hz, 7-20 V). The bradycardic responses were antagonized. Group III (M_3 receptor block): Acetyl β methylcholine (0.5-2µg/kg) induced hypotensive responses were antagonized. Group IV (Nnm) block: Blocking effects were determined by cumulative IV doses. ED50 values for block of the M_1, M_2, M_3 and Nnm responses were determined on at least 4 rats each. Results:

ED50 µg/kg* of Bis Tropacocainium Salts

Receptor	Chain Length C_3	C_4	C_6	C_7	C_9	C_{10}
M_1	-	70±5	-	7.4	-	12±1.1
M_2	60	70±16	30	17	16	25±3.4
M_3	1500	1100±100	1500	1000	400	150±36
Nnm	1300	1600±95	1400	800	600	600±43

*SEM's were calculated for all agents, example is given only with C_4 and C_{10}. ED50s of reference standards: Pyrenzipine (M_1) 7.6±0.6, AFDX-116 (M_2) 20±3.0, Atropine (M_3) 1.2±0.1, Atracurium (Nnm) 410±34.

Conclusion: These agents predominantly block M_1 and M_2 receptors and much less the M_3 and Nnm receptors.

Discussion: The parent compound, Tropacocaine (benzoyl β tropine) is quite weak in blocking M receptors. The present findings underline the previous suggestion that both Nnm and cardiac M_2 receptors may function in the form of twinned units (1). Interanionic distances of the functional groups of these receptors may be similar. The presence, type and/or steric position of additional groups (e.g. aromatic ester) may be a more discriminating probe between M_1, M_2 and Nnm receptors than the connecting chain between the N atoms. The type of quaternary ammonium group may be more important in achieving selectivity at M receptor subtypes.

Reference: (1) Eur. J. Pharmac 183/5 1987, 1990.

S98

TITLE: PROPOFOL-SUFENTANIL VS. ENFLURANE-SUFENTANIL ANESTHESIA IN CARDIAC SURGICAL PATIENTS: HEMODYNAMICS

AUTHORS: RI Hall MD, JT Murphy MD, EA Moffitt MD, RW Landymore MD, and the Maritime Heart Centre
AFFILIATION: Dept of Anaesthesia, Dalhousie University, Halifax, NS, Canada B3H 2Y9.

Supported by ICI Pharmaceutica, Wilmington, Delaware

Introduction: Controversy exists concerning the mechanism by which propofol produces hypotension.[1,2] Information concerning the use of propofol maintenance infusions in ASA III or IV patients is limited. This randomised trial in patients with preserved ventricular function (LVEDP<16, EF>40%) undergoing coronary artery surgery (CABG) compared the hemodynamic changes occurring during administration of propofol-sufentanil (PROP) vs enflurane-sufentanil (ENF) anesthesia.

Methods: Following informed consent and institutional approval, 47 patients (ASA II,n=1; ASA III,n=43; ASA IV,n=3) were studied. All chronic cardiac medications were continued and a standardised premedication given. Hemodynamic parameters (systolic (SBP), mean (MAP), and diastolic (DBP) systemic arterial pressure; mean (PAM), central venous (CVP) and pulmonary artery occlusion (PAOP) pressure; cardiac output (CO); systemic vascular resistance index (SVRI); and pulmonary vascular resistance index (PVRI)) were determined at the following intraoperative events: 1) awake, sedated (AWAKE); 2) post-induction (IND); 3) post-intubation (ETT); 4) first skin incision; 5) post-sternotomy; and 6) prior to cardiopulmonary bypass. PROP received sufentanil (SUF) 0.05 $mcg.kg^{-1}$ and propofol 1-2 $mg.kg^{-1}$ for induction and propofol 0.05-0.2 $mcg.kg^{-1}.min^{-1}$ infusion for maintenance anesthesia. ENF received sufentanil 5 $mcg.kg^{-1}$ for induction and enflurane 0.25-0.3% for maintenance anesthesia. Additional SUF (Max: PROP=5 $mcg.kg^{-1}$; ENF=7 $mcg.kg^{-1}$) was given for adverse hemodynamic responses. Between group differences were compared using a repeated measures analysis of variance technique ($p<0.05$).

Results: PROP produced hypotension on IND due to reduction in CI, SVI and SVRI (Table). At ETT, SVRI, HR and CI increased but SVI remained depressed indicating myocardial depression. Thereafter no differences were detected between the groups.

TABLE. Hemodynamic changes in cardiac patients receiving either propofol-sufentanil (n=24;PROP) or enflurane-sufentanil (n=23;ENF) anesthesia. (Mean±SD)

PARAMETER	AWAKE PROP	AWAKE ENF	IND PROP	IND ENF	ETT PROP	ETT ENF
SAP (mmHg)	156±22	152±26	104±20*	124±24	114±14	109±14
MAP (mmHg)	99±11	98±14	69±12*	82±12	78±11	76±9
DAP (mmHg)	71±10	72±10	52±10	62±9	68±14	65±9
HR (bpm)	63±11	55±16	65±11	73±19	78±24	77±17
SVRI($d.sec/cm^{-5}$)	761±256	720±156	569±233	536±133	678±264	580±184
CI ($l/min/m^2$)	2.88± 0.71	2.66± 0.51	2.67± 0.59	2.95± 0.58	3.11± 0.85	2.92± 0.73
SVI ($ml/b/m^2$)	46±8	42±9	42±8	42±10	42±10	40±11

*p<0.05 vs ENF and AWAKE

Conclusions: In these ASA III-IV patients having CABG, PROP-induced hypotension at IND was due to a reduction in SVR and myocardial depression. A maintenance infusion of PROP was hemodynamically well tolerated.

References:1. Anesthesiology 1989;71:260-77.
2. Anesthesiology 1990;72:393-4.

S99

THE EFFECT OF HEAVY AND LIGHT SMOKING ON PATIENT DURATION IN THE POST ANESTHESIA CARE UNIT

DS Handlin, MD and T Baker, MS
Department of Anesthesiology,
Monmouth Medical Center, Long Branch,NJ

Introduction: In a recent study that investigated the multifactorial parameters effecting patient duration in the post anesthesia care unit (PACU), we established a relationship between smoking and the length of time spent in the PACU.(1) In this present study, we investigated how the intensity of smoking affected the length of time the patient stayed in the PACU.

Methods: The approval of the Institutional Research Review Board was secured and 359 surgical patients were studied prospectively. Adults over age 18 yr receiving general anesthesia for all surgical procedures were included except open-heart and obstetrical, regardless of time or complexity. The intensity of smoking was measured on a scale of half packs of cigarettes smoked per day with no packs being 0 and four or more packs being 9. Sex, age, ASA physical status, surgical procedure, anesthesia time and PACU time were also recorded for each patient. Data were analyzed using ANOVA and Student's t tests with a significance of $\leq .05$.

Results: Of the 359 patients, 221 were nonsmokers and 138 were smokers with 21 smoking 0.5 pack per day (PPD), 25 smoking 1 PPD, 60 smoking 1.5 PPD, 17 smoking 2 PPD, 14 smoking 3 PPD and 1 smoking 4 PPD. Both groups were similar in age and weight. The entire smoking group spent significantly more time in the PACU than the nonsmokers (124±6 min [±SEM] and 111±4 min respectively), although the smokers had shorter anesthesia time than the nonsmokers (112±7 min and 137±6 min). Anesthesia time closely correlated with the length of PACU stay. The ratio of the PACU time to the anesthesia time, however, significantly differed between smokers and nonsmokers, 1.49±0.1 and 0.98±0.1 respectively. Among the various smoking groups, however, there was no significant difference in this ratio.

Discussion: The data from this study confirm that smoking increases PACU time. The data demonstrate that varying the degree of smoking from heavy to relative light does not negate the increased PACU time. This is significant since any degree of smoking must now be viewed as having serious consequences in the immediate postoperative period and must be discouraged. Further study is needed to evaluate the effect of short term smoking abstinence on duration of patient PACU stay.

References 1. DS Handlin, T Baker, J Woolwich: Effect of smoking on duration in recovery room. ASA Annual 1990 Meeting

S100

ROLE OF NERVE BLOCK AND EFFECT OF PAIN DURATION IN A CHRONIC PAIN POPULATION

DS Handlin, MD, T Baker, MS,
R Dworkin, PhD and D Richlin,MD
Department of Anesthesiology, Monmouth Medical Center, Long Branch, NJ 07740, Columbia University, New York, NY 10029 and Mt. Sinai Hospital, New York, NY 10032

Introduction: Anesthesiologists have long played a dominant role in the treatment of chronic pain due to their expertise in neural blockade and analgesic pharmacology. The question on when acute pain stops and chronic pain begins is difficult to resolve and accounts for the wide variations in the lower cut-off time for initial visits in different Chronic Pain Programs. This study seeks to define better this lower time limit as well as the importance of various treatment modalities on outcome in a chronic pain center.

Methods: Institutional Research Review Board approval and informed consent were secured from 454 consecutive chronic pain patients who were retrospectively studied. Pain variables as: duration, intensity, previous surgeries, work history, medications, mitigating and aggravating factors, etiology, treatment modalities and success were examined. Treatment success was evaluated using patient assessments and a composite evaluation of social function. Data were analyzed with ANOVA and CHI square analysis with a significance of .05.

Results: While patients seeking help had a range of 2 mo to 20 yr of pain with a median time of 2 yr, treatment success was found to decrease rapidly beyond 6 mo. All groups > 6 mo had similar treatment responses. Patients in the < 6 mo group had twice the success rate. These findings held true across a wide range of patient demographic factors. Among all modalities tested, neural blockade ranked highest in effectiveness. There was a significant relationship between number of nerve blocks and treatment success with the relative success rate of the nerve blocks series being >2.5 X than the no nerve block group.

Discussion: These results underscore the important contribution anesthesiologists can make to the care of chronic pain patients and emphasizes the need for their involvement in treating chronic pain. While duration has been cited as a factor in predicting patient outcome, the data of this study indicate that the earlier cut-off is a factor for maximum chance of improvement. This may be viewed as either a call for earlier pain clinic intervention or as support to those who set 6 mo as lower limit in defining the chronic pain patient.

S101

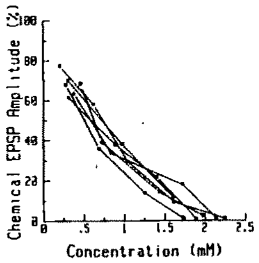
TITLE: SYNAPTIC MECHANISMS OF HALOTHANE ANESTHESIA

AUTHORS: K. Harada, M.D., T. Yamamura, M.D.
A. Okamura, M.D., O. Kemmotsu, Ph.D.
AFFILIATION: Dept. of Anesthesiol., Hokkaido Univ.
Sch. Med., N15 W7, Sapporo, 060 Japan

There is not yet agreement as to which element of the synaptic structure is the primary site of the action of anesthesia. To answer this, we studied the effects of halothane on the excitatory postsynaptic potential (EPSP) elicited by a single axon, postsynaptic responses to excitatory amino acids (EAAs) and activated membrane properties in giant interneurons (GIs) of the isolated spinal cord of the lampreys. They are one of the most primitive vertebrates, however, the synaptic physiology is similar to that in the higher vertebrates.

ED_{50} and ED_{90} of halothane on unitary EPSP amplitudes was 0.6mM and 1.8mM, respectively (Fig. 1). Halothane equally depressed the responses induced by EAAs in terms of the maximum depolarization as well as the maximum conductance increase (Fig. 2). ED_{50} and ED_{90} were similar to those in EPSP studies, thus, suggested that halothane inhibited the chemical synaptic transmission by postsynaptic mechanisms. Analyses of membrane properties showed that voltage-dependent sodium channels which generated an action potential were little affected at concentrations of halothane lower than 2 mM. Since the behavioral anesthetic ED_{50} and ED_{90} was 0.25 mM and 0.5mM, respectively, anesthesia could be produced by only slight inhibition of chemical synaptic transmission.

The present results supported an idea that the primary active site of inhalation anesthetics was at EAA receptors.



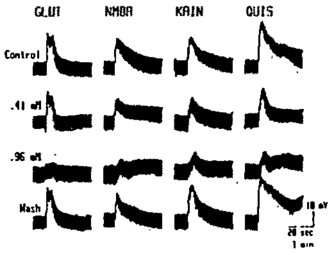


Fig. 1 (left): Effects of halothane on a unitary EPSP. Data obtained from 6 axon-GI pairs were normalized to percent of the control values as a function of halothane concentration.

Fig. 2 (right): The response to bath-applied EAAs in a GI in Mg^{2+}-free, TTX and 4-AP containing perfusate. To measure the membrane conductance change, hyperpolarizing current pulses -10 nA, 60 msec were applied at a frequency of 1 Hz (GLUT) or 0.3 Hz (others). GLUT: glutamate, 500uM. NMDA: N-methyl-D-aspartate, 500uM. KAIN: kainate, 50uM. QUIS: quisqualate, 50uM. The gaschromatographically determined concentration of halothane is labeled at left.

Reference
Anesthesiology 72:704-710, 1990.

S102

Title: DOES OMEPRAZOLE, A GASTRIC ACID PUMP INHIBITOR REDUCE GASTRIC VOLUME AND ACIDITY IN OUTPATIENTS?

Authors: DA Haskins MD, JS Jahr MD, U Ramadyhani MD, M Texidor PhD, D Kelley BS
Affiliation: Department of Anesthesiology, Tulane University Medical Center, New Orleans, Louisiana

Introduction: A retrospective study of 185,358 anesthetics reported aspiration incidence of 1:2131 with mortality of 1 in 46,340 anesthetics.[1] Patients with a gastric pH below 2.5 and a volume of 0.4 $ml \cdot kg^{-1}$ or greater are at risk of developing severe aspiration pneumonitis, if aspiration occurs.[2] Omeprazole is a recently released, FDA approved, substituted benzimidazole; it causes dose-dependent intracellular inhibition of gastric acid secretion in humans. This study examined the effect of omeprazole in decreasing gastric acidity and gastric residual volume in outpatient adults in a double blinded manner.

Methods: After IRB approval and patient consent, unpremedicated outpatients, ASA I-III, 18 years or older (n=17), were randomly assigned to either of two groups. Group I received omeprazole 80 mg, and group II received placebo by mouth the night before scheduled elective outpatient surgery. Exclusion criteria were: gastric motility, acid secretory disorders, renal or hepatic disease, obesity, mental incompetence, clinically significant bleeding disorders. Anesthesia was induced with thiamylal (3-4 $mg \cdot kg^{-1}$); appropriate muscle relaxant was given to facilitate endotracheal intubation. After the patient was anesthetized, an orogastric tube was inserted with proper placement verified by auscultation for gastric sounds. Gastric residual contents were withdrawn into a Luken's trap, and pH was then determined and gastric volume indexed to weight ($ml \cdot kg^{-1}$). Patients were assessed for nausea and vomiting in the PAR and at 24 hours postoperatively. Data were analyzed by a t-test, with a $p<0.05$ considered statistically significant.

Results: Patient characteristics of both groups were similar. There was a significant difference between the two groups for pH ($p=0.02$) but no statistical difference between the two groups for volume indexed to weight ($p=0.07$, see Table).

Discussion: Omeprazole 80 mg, by mouth inhibits 99% of pentagastrin stimulated acid secretion with an 87% reduction in gastric volume.[3] This study demonstrated a statistically significant increase in gastric pH and a clinically significant decrease in gastric residual volume in patients given 80 mg of omeprazole the night before surgery compared to controls given placebo.

TABLE Gastric pH and Volume Data

	Gastric pH mean±SEM		$ml \cdot kg^{-1}$ mean±SEM	
Omeprazole	4.56	0.76	0.24	0.06
Placebo	2.05	0.37	0.43	0.08
	$p=0.02$		$p=0.07$	

References: 1. Olsson GL, Hallen B, Hambraeus-Jonzon K. Aspiration during anaesthesia: a computer-aided study of 185 358 anaesthetics. Acta Anaesth Scand 1986;30:84-92.
2. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. Anesth Analg 1974;53:859-868.
3. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole-a gastric proton pump inhibitor-on pentagastrin stimulated acid secretion in man. Gut 1983;24:270-276.

S103

TITLE: CARDIOVASCULAR AND CENTRAL NERVOUS SYSTEM EFFECTS OF BUPIVACAINE IN MAGNESIUM DEFICIENT RATS

AUTHORS: J Heavner PhD[1], F Zavisca MD[1], JM Badgwell MD[1], M Boylan PhD[2], P Rosenberg MD[3]
AFFILIATION: Anesthesiology, TTUHSC[1], Nutrition, TTU[2], Lubbock, TX, and U of Helsinki, Finland[3]

Magnesium deficiency can produce seizures[1] and can induce cardiac arrhythmias[2] similar to those caused by bupivacaine (BUPI). The objective of this study was to determine if magnesium deficiency enhances the central nervous system (CNS) and/or cardiotoxicity of BUPI.

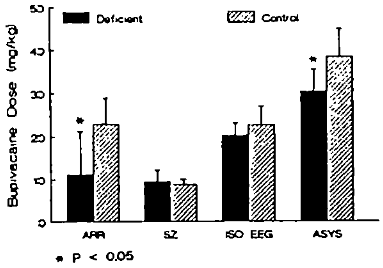
After approval from the Animal Care and Use Committee, we studied 15 Sprague Dawley rats 7 weeks of age. Eight were maintained on a Mg deficient (MgD) diet and 7 were maintained on a normal rodent (C) diet for 4 weeks. Then, anesthesia was induced using halothane and the trachea intubated. Ventilation was controlled to maintain arterial PCO_2 at 32-36 mmHg. The electrocardiogram, electroencephalogram (EEG), and arterial blood pressure were continuously recorded. The rats were paralyzed with pancuronium and stabilized for 30 minutes on 70% N_2O/30% O_2, 0.5% halothane then continuously infused with BUPI at a rate of 2 mg/kg/min. Results were examined using one-way ANOVA and the Student-Newman Keuls test.

All animals had cardiac arrhythmias (ARR) seizures (SZ), isoelectric EEG (ISO EEG), and asystole (ASYS) during BUPI infusion. The MgD animals had a slower weight gain than did the C rats. The MgD animals developed skin lesions on the head and neck and were more active than were the animals in the C group. Bupivacaine doses producing cardiac arrhythmias and asystole were significantly lower ($P<0.05$) in the MgD as compared to C rats (Fig.).

Magnesium deficiency apparently enhances the cardiotoxity of BUPI without affecting its CNS toxicity.

References:
1. Tancredi V: Brain Res 1990; 511:280-290
2. Rankin AC, et al: Am Heart J 1990; 119:185-186

DOSES OF BUPIVACAINE FOR TOXIC ENDPOINTS + S.D.



S104

LOSS OF CARDIAC EFFECTIVITY WITH CATECHOLAMINES IN HYPOTHERMIA - THREE DISTINCT MECHANISMS IN SHEEP

Carl F Heidelmeyer MD, Thomas Schroeder MD, Jens P Hering, Siegfried Veit MD, Gerhard Hellige MD
Dept. Anaesthesiology, UKRV-Charlottenburg, FU Berlin, Dept. Physiology, Georg-August-Universität Göttingen, West Germany; supp. by the DFG: SFB 330 Organprotektion

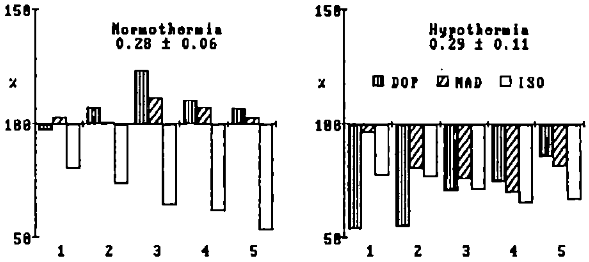
Introduction. Hypothermia is usually employed to reduce metabolic demand in conditions of impaired organ perfusion. As cardiovascular pharmacotherapy is often required in both accidental and induced hypothermia, we investigated the pharmacological actions of three catecholamines.

Methods. After approval by the committee for animal research, six anaesthetized sheep (median 45.8kg) were evaluated using a standard closed chest model [1]. Basal anaesthesia was maintained with an infusion of midazolam (0.36mg/(kg·h)) and buprenorphine (7.2 g/(kg·h)) and at half these rates during hypothermia. Controlled ventilation with an oxygen/air mixture was performed to an alpha-stat regimen. Recording of the haemodynamic data was performed with standard equipment; coronary sinus blood flow was diverted and measured extracorporeally. Catecholamines were applied for 3 to 4 minutes at each of 5 incremental dosages :

Medication	Abbrev.	microgramme/min				
Noradrenaline	NAD	20	40	60	80	100
Isoprenaline	ISO	6	12	18	24	30
Dopamine	DOP	600	1200	1800	2400	3000
Dosage (see figure):		1	2	3	4	5

The catecholamines were given both at 29°C and 39°C body temperature, each animal serving as its own control.

Results. Under haemodynamic control conditions the reduction of body temperature by 10°C reduced total body oxygen consumption by 48% and was accompanied by a decrease in heart rate of 24%. Cardiac output (co), aortic and pulmonary artery pressures were maintained within ±10%. Despite a dP/dt increase of 73%, myocardial oxygen consumption decreased marginally (7%). Cardiac effectivity, calculated as the ratio of external work to caloric (oxygen) uptake, was not significantly changed. However, with the infusion of the sympathicomimetics cardiac effectivity was greatly reduced :



Discussion. Hypothermia reduces the chronotropic effect of ISO and therefore loss of cardiac efficiency is less. However, in hypothermia, with diminished CNS cardiovascular control, NAD induced unmitigated vasoconstriction; high afterload and decreasing co explain the loss of cardiac function. Asynchronous myocardial contraction, observed only with dopamine in hypothermia [2], is a third contributing factor reducing cardiac effectivity. With other catecholamines mixed responses according to the α/β ratio can be expected.

Ref. [1] Anesth Analg 70: S152, 1990. [2] Europ J An 7: 337, 1990.

S105

TITLE: A COMPARISON OF LIDOCAINE, FENTANYL AND ESMOLOL IN THE PREVENTION OF INTUBATION RELATED TACHYCARDIA AND HYPERTENSION

AUTHORS: S.M. Helfman, M.D., M.I. Gold, M.D., E.A. DeLisser, M.D., C. Herrington, R.N.
AFFILIATION: Anesthesiology Depts. Univ. of Miami School of Medicine and VA Medical Center, Miami, FL 33125

Hypertension and tachycardia usually accompany laryngoscopy and tracheal intubation. Various agents are used in an attempt to blunt this response, with fentanyl[1] and beta blockers[2] most successful.

A double blind, placebo controlled study was conducted to compare the effectiveness of post-induction, single bolus placebo (PLAC), lidocaine (LIDO), fentanyl (FENT), and esmolol (ESM) in blunting the intubation response. After institutional approval and written informed consent, 80 patients, ASA class II - IV, scheduled for non-cardiac surgery were randomly assigned to receive a preintubation dose of 15 cc of PLAC, LIDO 200 mg, FENT 200 mcg, or ESM 150 mg. Induction was accomplished with bolus thiopental 4-6 mg/kg, followed immediately by the study drug; succinylcholine 1-1.5 mg/kg was given at min 1. Laryngoscopy and intubation was performed 2 min following induction, and the patient was maintained on 1 MAC ± 10% isoflurane in 60% N_2O/O_2 for 10 min. Heart rate(HR) was recorded every 15 seconds and blood pressure(SBP) every minute from induction until 10 min after intubation. ANOVA and the Newman-Keuls multiple range test were used to compare each group with each of the others at each event. Results were significant if $p < 0.05$.

Demographics and baseline HRs and SBPs were statistically similar in each of the 4 groups. Maximum percent increase in HR (mean ± S.E.) following intubation was similar in the PLAC (44 ± 6), LIDO (51 ± 10) and FENT (37 ± 5) groups, but was lower in the ESM (18 ± 5) group ($p < 0.05$). SBP percent increases were lower in the LIDO (20 ± 6), FENT (12 ± 3), and ESM (19 ± 4) groups than in the PLAC (36 ± 5) group ($p < 0.05$), but not different from each other ($p > 0.05$).

Only ESM provided consistent and reliable protection against both HR and SBP increases accompanying laryngoscopy and intubation. LIDO and FENT failed to protect against HR increases compared to PLAC. The three agents worked equally well in blunting SBP increases.

References

1. Anesth Intens Care 16:411-417, 1988
2. Anesth Analg 68:S133, S134, 1989

S106

Title: EFFECTS OF FENOLDOPAM ON CEREBRAL AUTOREGULATION AND CO_2-REACTIVITY IN SWINE

Authors: H.J.HENNES, M.D.; J.P.JANTZEN, M.D.; W.DICK, M.D.
Affiliation: Dept. of Anesthesiology, Johannes Gutenberg University, Mainz, FRG

Introduction: The new selective dopamine A_1-receptor agonist fenoldopam (FE) was found to be effective in treatment of malignant hypertension. FE increases renal blood flow and urinary output (1). However, no information is yet available on its intracranial effects. We studied the influence of FE on intracranial pressure (ICP), intraocular pressure (IOP), and on autoregulation and CO_2- reactivity of intracranial vessels.

Methods: After approval by the institutional animal investigation committee 7 German landrace piglets (23-29 kg) were premedicated (azaperone 8 mg/kg i.m.), anesthetized (piritramide; induction 1 mg/kg i.v.; maintenance: 2 mg/kg/h), intubated, artificially ventilated and instrumented (arterial line, Swan-Ganz catheter, lateral ventricle catheter, ocular anterior chamber cannula). Ventilation (60 % N_2O in O_2) was controlled by end tidal capnometry. 30 minutes after commencing an i.v. infusion of FE 4 µg/kg/min CO_2-reactivity was tested by elimination and reintegration of soda lime canisters. Cerebral autoregulatory response was analyzed by infusion of angiotensin II (AN). Cerebral perfusion pressure (CPP) was calculated using standard formulae. Statistical evaluation utilized Student's t-test and analysis of variance (ANOVA) where appropriate.

Results: Means ± SEM [mm Hg]

	CPP	ICP	IOP
Control	80 ± 2	14 ± 2	21 ± 2
FE	58 ± 1*	17 ± 1	22 ± 2
FE + AN	130 ± 6**	19 ± 2	43 ± 2**
FE	67 ± 4*	19 ± 2	23 ± 1
FE + CO_2	55 ± 4*	24 ± 1**	21 ± 2
FE	66 ± 3*	16 ± 1	21 ± 2

*: $p < 0.05$ vs. control; **: $p < 0.05$ vs. FE

Discussion: In our porcine model, the continuous infusion of FE produces a dose dependent vasodilation, resulting in a reduction of MAP with reflex tachykardia. FE causes no rise in ICP, but there are indicators of a decreased intracranial compliance. Autoregulation and CO_2-reactivity of the cerebral vessels are not compromised during FE administration. At the time being, caution should be exercised when infusing FE in patients with reduced intracranial compliance.

References:

1. J Clin Anesth 1: 66 (1988)

S107

TITLE: EVALUATION OF OPERATIVE RISK IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

AUTHORS: T Higgins MD, FG Estafanous MD, FD Loop MD, J Blum, GJ Beck PhD

AFFILIATION: Departments of Cardiothoracic Anesthesia, Thoracic/Cardiovascular Surgery, and Biostatistics/Epidemiology, Cleveland Clinic, Cleveland OH 44195

Introduction: Anesthesiologists are called upon to prospectively assess risk in cardiac surgical patients, but are limited since most patients fall into ASA categories III and IV. We have developed a new system for risk assessment in this population that stratifies risk based on multiple, readily available preoperative factors.

Methods: Prospective data on 5033 consecutive patients undergoing CABG (including those with concurrent carotid or valve procedures) was analyzed for factors contributing to morbidity or mortality by univariate analysis and logistic regression. A simplified clinical scoring system was developed based on logistic regression results.

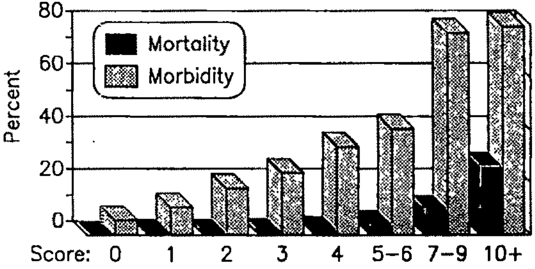
Results: Logistic regression identified emergency procedure (hemodynamic instability or on IABP), left ventricular (LV) dysfunction (ejection fraction <35%), elevated preop serum creatinine (psCr), preop hematocrit (pHct) ≤34%, age, prior heart operation, weight ≤65 kg, chronic pulmonary disease (COPD) or prior lung surgery, prior vascular surgery, and mitral valve (MV) insufficiency to be predictors of mortality. In addition to these factors; mitral stenosis, aortic (Ao) insufficiency, Ao stenosis, history of myocardial infarction (MI) with congestive failure (CHF), female gender, and diabetes mellitus were significant predictors of morbidity (stroke, ventilator dependency >72 hrs, renal failure, infection, low cardiac output or death). Based on odds ratios, these factors were assigned points (Table). The relationship between score and morbidity and mortality is shown in the graph. The model fits the data well by Hosmer-Lemeshow goodness-of-fit. Negative predictive value for mortality up to a score of 5 is 99.2%. By receiver-operating characteristic analysis, the logistic and clinical mortality models have an area under the curve of 0.84.

Discussion: This index estimates risk of morbidity and mortality based on easily retrievable preoperative clinical information, and is more sensitive than the method used by the Health Care Financing Agency (1). By accounting for the patient's preoperative physiologic condition, the effects of surgical, anesthesia and ICU care can be better assessed. Although this index is insufficiently sensitive for individual prognosis, it may assist in more realistic estimation of outcome than presently available methods, including ASA score. Prospective multi-institution validation is planned.

Reference: 1) Green J, Wintfeld N, Sharkey P et al: The importance of severity of illness in assessing hospital mortality. J Am Med Assoc 263:241, 1990.

Table: Points assigned for each factor

Emergency case	5	COPD or prior lung surgery	2
LV Dysfunction	3	Prior vasc surgery	2
psCr > 2.0 mg/dl	4	Mitral insufficiency	2
psCr 1.8-1.9 mg/dl	2	Mitral stenosis	1
psCr 1.6-1.7 mg/dl	1	Aortic insufficiency	1
pHct < 34%	2	Aortic stenosis	1
Age > 75 years	2	Hx MI and CHF	1
Age 65-74 years	1	Female gender	1
Prior Heart Surg	2	Diabetes mellitus	1
Weight ≤65 kg	1		



S108

Title: DIRECT MEASUREMENT OF CANINE PULMONARY MICROVASCULAR COMPLIANCE.

Authors: S.C. Hillier, M.B.,Ch.B., R.G. Presson,Jr., M.D., P.S. Godbey, B.S., O. Okada, M.D., W.W. Wagner, Jr.,Ph.D.

Affiliation: Departments of Anesthesia, Physiology & Biophysics, Indiana University, Indianapolis, IN.

Introduction: The compliance of the pulmonary microcirculation is an important determinant of pulmonary hemodynamics. However, until recently direct measurement of pulmonary microvascular pressure/volume relationships have not been possible. This data is essential for understanding the role of microvascular compliance changes in disease states such as pulmonary hypertension and the microvascular response to anesthetic and vasoactive drugs. We have developed the first method to determine pulmonary microvascular compliance using videomicroscopy of the isolated perfused lung.

Method: This study was performed with the approval of our animal care committee. The left lower lobe was excised from pentobarbital anesthetized dogs (21-24 kg) and perfused with heparinized autologous blood at 37°C. The lobes were ventilated with 17%O_2/6%CO_2/77%N_2 to maintain normal blood gases. Blood flow in a subpleural arteriolar and venular pair (both <50µm diameter) was videotaped through a microscope. Perfusion of the lobe was increased in a stepwise manner and then similarly decreased to produce an increasing and decreasing series of microvascular pressures, measured using a double occlusion technique[1]. Vessel diameters were determined from analysis of the videotape. Compliance curves were constructed by plotting percentage change in vessel diameter against microvascular pressure (see figure).

Results: Over the range of pressures studied, there was a linear relationship between vessel size and pressure. When the vessel diameters were compared at increasing and decreasing pressures, there was no evidence of hysteresis. There was no significant difference between venular and arteriolar compliance over the range of pressures studied (paired t-test).

Conclusion: This method permits direct measurement of the changes in microvessel diameter that occur as micro-vascular pressure changes. Investigations are in progress to determine directly the effects of anesthetic and vasoactive agents on pulmonary microvascular dynamics. Further study over a greater range of pressures is needed to determine if the microvascular pressure/volume relationships remain linear under different conditions.

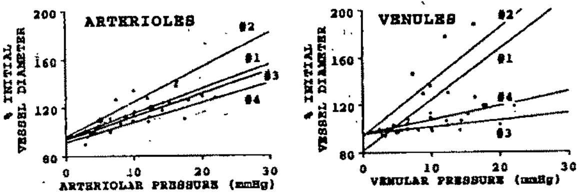


Figure: Arteriolar and venular compliance data are shown for 4 isolated lobe preparations (#1 to #4). (r for arterioles = 0.90-0.92, for venules = 0.59-0.91)

Reference: Hakim.T.S., Kelly.S. J.Appl.Physiol.67: 1277-1285, 1989.

S109

Title: PRESSURE TRANSDUCER PERFORMANCE INSIDE A MAGNETIC RESONANCE IMAGING SCANNER.

Authors: S.C. Hillier, M.B.Ch.B, R.G. Presson,Jr, M.D. K.A. Haselby, M.D., C.C. Rao, M.D.
Affiliation: Department of Anesthesia, Indiana University School of Medicine , Indianapolis, IN.

Introduction: The use of Magnetic Resonance Imaging (MRI) is increasingly common in critically ill patients. The management of these patients often requires that invasive pressure monitoring be continued during the procedure. Non-ferromagnetic pressure transducers are safe for use in the presence of a large magnet[1]. However, we are aware of no data concerning the accuracy of pressure transducers when within an MRI magnet. An instance of pressure transducer malfunction during MRI scanning experienced by our group led us to perform the following study.

Method: A Bio-Tek 601A pressure waveform generator was used to simulate an arterial waveform. The pressure generator was connected to an American Edwards Trantec® transducer via 8 meters of pressure monitoring tubing. The transducer output was measured by a Datascope 870 monitor and pen recorder located 12 meters from the magnet in an adjacent room. After zeroing and calibration, the transducer was placed 4.5 meters from, 2 meters from, and finally within the center of the 1.5 Tesla magnet while recordings were made of the generated waveform. At each location the transducer was also opened to the atmosphere to determine if zero drift had occured. The position of the monitor/pen recorder and waveform generator was held constant during the study. The scanner was then activated to determine the effect of radio-frequency (RF) interference on pressure waveform and to determine if the transducer had produced any image degradation.

Results: The pressure waveform morphology did not change as the transducer was introduced into the magnet. However, as the transducer approached the magnet a substantial zero drift occurred which accounted for a 50mmHg increase in systolic and diastolic pressures when the transducer was at the center of the magnet (figure). The gain of the transducer was unaffected. When the MRI was activated there was no significant RF interference. If the transducer was re-zeroed within the magnet the measurements returned to normal. There was no evidence of scanner image degradation by the transducer.

Discussion: We describe a significant measurement error that may be overcome by placing the tranducer away from the center of the magnet and/or by re-zeroing the transducer in its final scan position. An alternative solution is to move the transducer further from the patient, however the use of longer pressure tubing alters the frequency response and damping characteristics of the system, thereby introducing other errors . The performance of other transducers in MRI scanners is yet to be investigated.

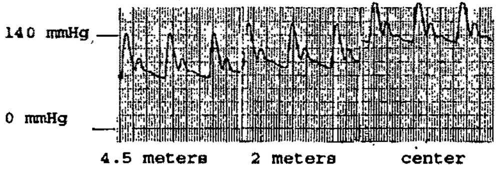


Figure: Arterial waveforms from a transducer located 4.5 meters from, 2 meters from, and within the magnet.

Reference: Blitt, C.D. Monitoring in Anesthesia & Intensive Care. p688. Churchill Livingstone 1990.

S110

TITLE: A METHOD TO REDUCE PACU COMPLICATIONS: MONITORING LOWER ESOPHAGEAL CONTRACTILITY

AUTHORS: R. Hines, M.D., C. Rinder, M.D., A. Perrino, M.D., T. O'Connor, M.P.H., A. Lippman, R.N.
AFFILIATION: Dept. Anes., Yale Univ. School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

INTRODUCTION. One of the most frequently encountered complications occurring in the post anesthesia recovery room (PACU), is the need for continued upper airway support.[1] Lower esophageal contractility (LEC) has been shown to be a reliable method for assessing anesthetic depth.[2] The present study was designed to test the hypothesis that the use of LEC could result in a decrease in the incidence of prolonged upper airway support.

METHODS. Following approval of the Human Investigation committee, a prospective study of 200 patients undergoing general anesthesia was performed. All patients studied were ASA status I, II, or III undergoing orthopedic or abdominal surgery. Inclusion criteria were: primary inhalational anesthetic technique with a duration of ≤4 hrs. Induction and intubation techniques were standardized. Muscle relaxation consisted of vecuronium or pancuronium. Maintenance anesthesia was by inhalational agents. Ventilation was controlled to maintain normocapnia.

In the study group, (n=100) following intubation, a disposable esophageal contractility probe was inserted. LEC was measured using the Lectron 302 monitor (American Antec) and probe equipped with two balloons: a proximal air filled distending balloon used to provoke contraction from the lower esophagus (PLEC) and a distal fluid filled sensory balloon for measuring spontaneous lower esophageal contraction (SLEC). The probe was inserted to a reference point, and the distal balloon was attached to a pressure transducer. Total LEC was calculated and displayed as the esophageal contractility index (ECI); ECI=70 x SLEC+PLEC. A control population (n=100) matched for ASA status, and duration of anesthesia was not monitored with LEC. The incidence of upper airway support in the PACU was recorded by the nursing staff who were blinded to the presence or absence of intra-operative LEC. In all patients time to extubation and need for upper airway support in the PACU was recorded. Data was analyzed using chi square, and analysis of variance with P<0.05 considered significant.

RESULTS. The overall incidence of upper airway support in the PACU was 18.32%. In the study group, using LEC monitoring, only 0.86% of patients required prolonged airway support. In the control group 9.72% of patients required airway support.

DISCUSSION. The data from this study reveal that the frequency of prolonged upper airway support in the PACU is decreased by using LEC monitoring. Previous studies have documented the advantages of LEC monitoring in accessing anesthetic depth. Our results show that the use of LEC demonstrates a reduction in one of the most frequently encountered PACU complications.

PACU Upper Airway Support (%)

Overall	Study Group (+ ECI monitor)	Control Group (- ECI Monitor)
18.32%	0.86%*	9.72%

*p<.005

References.
1. Anesthesiology 67(3A) A471, 1987.
2. Lancet May 1987 pp. 1151-1154.

S111

Title: **Effects of Succinylcholine on the Recovery of Vecuronium-induced Neuromuscular Blockade**

Authors: S.T. Ho, M.D., B.H. Lin, M.D., W. Ho, M.D., C.Y. Lin, M.D.

Affiliation: Department of Anesthesiology, National Defense Medical Center, Taipei, Taiwan, Republic of China
Department of Anesthesia and Critical Care, University of Chicago, Chicago, Il.

Introduction: If abdominal relaxation is inadequate at the end of surgery, a transient increased neuromuscular (NM) blockade is needed to facilitate closure. Succinylcholine (Sch) is the only currently available agent with a short duration of action that enhances NM blockade by atracurium.[1,2] The present study was designed to investigate the effects of Sch on the recovery from NM blockade induced by vecuronium (Vec).

Methods: After Institutional Review Board approval, 70 ASA I-II unpremedicated patients were randomly allocated into 7 groups of 10 each. Before anesthesia, no patients received drugs that affect NM transmission. Anesthesia was induced with thiopental and fentanyl, and tracheal intubation was facilitated by Vec 0.1 mg/kg. Anesthesia was maintained with 66% nitrous oxide and 0.5-1.5% isoflurane in oxygen. During anesthesia, blood pressure and ECG were monitored and end-tidal CO2 was maintained at 30-40 mmHg. By means of a Datex Relaxograph, control records of the integrated electromyographic responses to train of four supramaximal stimulation at the ulnar nerve were obtained after the induction of anesthesia and before the administration of Vec. Once the first twitch (T1) recovered to 50% of control, groups I-VII were given one of seven different doses of Sch: 0.4, 0.6, 0.8,1.0, 1.2, 2.0, or 3.0 mg/kg. The effects of Sch on residual NM blockade by Vec were recorded. These variables of recovery included changes in T1, duration of blockade (from injection of Sch to T1, which restored the previous estimated recovery curve of Vec), and recovery index (T1 25-50%). After receiving Sch, 18 patients from groups V and VI were randomly subdivided into two groups that were given neostigmine or edrophonium to reverse the residual NM blockade by Vec and Sch. Comparisons between groups were made using a one-way analysis of variance (significance: $p < 0.05$).

Results: Sch 0.4 mg/kg antagonized NM blockade by Vec (13.6%), but 0.6 to 3.0 mg/kg Sch significantly enhanced blockade (12.7% to 50.0%). T1 25%-50% of Vec and Sch was 1.7 to 2.1 minutes and duration was 5.2 to 14.1 minutes, which were dose-dependent. Neostigmine and edrophonium effectively reversed the residual NM block by Vec and Sch from train-of-four ratio 34.0% and 55.5% to 90.9% and 98.2%, respectively.

Discussion: The study demonstrates that Sch (0.6 mg/kg) is able to enhance residual NM blockade by Vec for more than 5 minutes, and neostigmine or edrophonium effectively reverse NM blockade by Vec and Sch. This phenomenon is probably explained by rapid hydrolysis of Sch. It is concluded that Sch can be used to facilitate closure in case of inadequate abdominal relaxation but does not interfere with reversal of Vec-induced NM blockade.

References

1. Anesthesiology 43:236,1975.
2. Br J Anaesth 61:292,1988.

S112

Title: CEREBRAL PERFUSION WITH SALINE IMPROVES OUTCOME FROM INCOMPLETE ISCHEMIA IN RATS

Authors: W.E. Hoffman, Ph.D., R.L. Ferguson, M.D., D.J. Miletich, Ph.D., R.F. Albrecht, M.D.

Affiliation: Dept. of Anesthesiology, University of Illinois-Chicago/Michael Reese Hospital, Chicago, Illinois

Introduction: Incomplete ischemia is associated with sludging of blood in cerebral vessels and hypoperfusion of the brain in the recovery period. We carried out experiments to determine whether intracerebrovascular saline perfusion during incomplete ischemia may improve outcome by improving post-ischemic cerebral perfusion.

Methods: After approval from the Institutional Animal Care Committee, Male Sprague-Dawley rats, 350-450 g, were anesthetized with isoflurane intubated and mechanically ventilated with 2% isoflurane in air. Catheters were inserted into the right femoral artery, the left femoral vein and the external jugular vein for blood pressure recording, drug administration and blood withdrawal. In control and sham treated rats (n=10 per group), the right carotid artery was ligated. In cerebral perfused rats (n=10) the carotid was catheterized retrograde to allow brain perfusion during ischemia. Ischemia was produced by right carotid occlusion combined with hemorrhagic hypotension to a MAP of 30 mmHg with a range of 2 mmHg for 30 minutes. Anesthesia was maintained at 1.4% isoflurane in room air and rectal temperatures at 37^{o}C throughout the experiment. Arterial pH was maintained at 7.40 by bicarbonate infusion and $PaCO_2$ at 35-40 mmHg by adjusting ventilation. Cerebral perfused rats were infused with saline warmed to body temperature into the carotid artery at a rate of 0.3 ml/min during ischemia. Sham treated rats were infused iv with saline at a rate of 0.3 ml/min during ischemia and control rats received ischemia without saline infusion. After ischemia the rats were recovered and evaluated for neurologic outcome for 3 days using an 18 point neurologic exam. The rats were then killed and the brains examined for histopathologic damage.

Results: During ischemia, rats infused with saline into the ischemic brain and rats infused with saline iv had a decrease in hematocrit compared to control rats. Other physiological parameters, including plasma glucose, were similar between the 3 groups. Neurologic outcome and histopathologic damage were significantly improved in cerebral saline perfused rats compared to control and sham treated rats.

Discussion: These results show that cerebral perfusion with saline improves outcome from incomplete ischemia. This was not due to a decrease in hematocrit since outcome was not improved in sham treated rats. Cerebral saline infusion may improve outcome by improving post-ischemic microvascular perfusion. Preliminary experiments measuring tissue perfusion indicate that brain saline infusion does not alter cerebral blood flow during ischemia.

S113

TITLE: **PENTAMORPHONE VS. FENTANYL IN BALANCED ANESTHESIA DURING GENERAL SURGERY**

AUTHORS: **M.B. Howie, M.D., J.A. Duarte, M.D., G.D. Rypel, M.D., V.A. Romanelli, M.D., A. Rezaei, B.A.**

AFFILIATION: **Department of Anesthesiology, The Ohio State University Hospitals, Columbus, Ohio 43210**

Introduction: Pentamorphone is a morphinan derivative narcotic. Based on animal studies pentamorphone (P) has been reported to have analgesic potency two to eight times greater than that of fentanyl (F). Proceeding on this information we performed a randomized double-blind isoflurane (Iso) sparing study in healthy surgical patients who were given pentamorphone or fentanyl as the analgesic during general anesthesia. Anesthetic potency can often be ascertained from patients' hemodynamic responses. We compared the hemodynamic profiles and the supplemental dose requirements of fentanyl vs. pentamorphone during general anesthesia.

Methods: Fifty consenting adults were randomized with institutional approval to receive a loading dose of 1 ug/kg of pentamorphone or 7.5 ug/kg of fentanyl just before the induction of anesthesia with thiopental and succinylcholine. A 70/30% mixture of N_2O/O_2, and vecuronium were used for maintenance. Isoflurane was administered for a greater than 15% rise in blood pressure. Recovery parameters, nausea, need for analgesics, or need for antiemetics were recorded. The number of supplemental doses of 0.15 ug/kg P or 1.5 ug/kg F were also recorded. Strict exclusionary criteria and biochemical testing were used to assure normal health.

Results: Both analgesics were clinically satisfactory. Pentamorphone, however, had some strikingly notable differences to fentanyl. Patients receiving calculated equipotent doses of pentamorphone did not need any Iso supplementation until 34 minutes into the anesthesia, while the F group required Iso at 4 minutes. The total Iso time for the F group was 30 minutes compared to 8 minutes for the P group. The morphine requirement postoperatively for F was also ten times greater than P. Postoperative nausea was significantly lower in the P patient group.

Demographic analysis of the data showed no statistical differences between groups. The hemodynamic profiles of the two groups showed no statistical significance between DAP, SAP, MAP, or HR. The required number of supplemental narcotic doses was higher in the F group compared to the P group. The time between supplemental narcotic doses was longer in the P group. Isoflurane administration occurred earlier in the F group; blood pressures were equally controlled in both groups in the presence of intermittent Iso. Nausea, vomiting, and recovery times were equal.

Discussion: Ideally, any new analgesic should provide an advantage over previously available opiates. Pentamorphone has been shown to decrease isoflurane and postoperative analgesic requirements compared to F. These advantages have not been achieved at the expense of recovery times and P has no more, and possibly less, respiratory depression in the immediate postoperative period while still retaining its analgesic action.

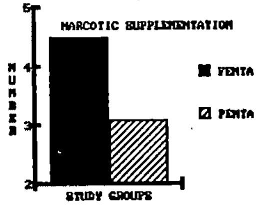
Conclusion: We utilized a potency ratio of 7.5/1 P to F. Within this protocol, patient acceptance was satisfactory in both groups. Furthermore, the fact that the P group received less narcotic and inhalational supplementation suggests that pentamorphone is better at blunting the hemodynamic response to surgery while providing a satisfactory postoperative side effect profile.

Based on simple clinical criteria in an adequate number of healthy volunteers P is a very satisfactory opiate analgesic. It is extremely potent and if its isoflurane sparing properties are taken into account, its potency ratio in humans should be revised upwards.

Clinical Observations:

	Fenta (n=22)	Penta (n=28)
Time: (min)		
From induction to when Iso given	4.0± 2.1^A	34.2±18.4^A
Total Iso time	31.0±10.3^A	7.8±4.4^A
To awake after N2O stopped	2.0±1.4	2.6±1.5
Recovery room Morphine (mg)	5.0±2.2^A	0.4±0.9^A

Note: A indicates a significant difference (P<0.05)



S114

Title: **TITRATION OF BARBITURATE CEREBRAL PROTECTION TO AN ISOELECTRIC EEG PRIOR TO CIRCULATORY ARREST**

Authors: **M.B. Howie, MD, T.A. Galbraith, MD, V.A. Romanelli, MD, G.D. Rypel, MD, M.G. Guertin, MD, T.D. McSweeney, BS**

Affiliation: **Depts. of Anesthesiology and Cardiothoracic Surgery, The Ohio State University Hospitals, Columbus, Ohio 43210**

Introduction: In operative procedures such as aortic arch repair where it is necessary to stop the circulation, brain protection must be provided against ischemic insult.

The use of hypothermia by itself does not ensure cerebral protection. Barbiturates are added in large doses to enhance cerebral protection. These large doses prolong recovery from anesthesia and require vasotonic drugs and long postoperative ventilation.

This study examines a physiological endpoint for the titration of thiopental at a predetermined and stable degree of hypothermia prior to cessation of the circulation.

Methods: Fourteen consenting patients for aortic arch repair had a 16 lead EEG placed prior to standard narcotic induction of anesthesia. The patients were cooled on CPB to approximately 20° C, and thiopental was administered in 400 mg increments until isoelectric readings were maintained in all EEG leads. The patients were closely followed postoperatively for time to awakening, time to extubation, and neurological status.

Results: A mean dose of 18.2 mg/kg of thiopental was administered at a temperature of 18.5°C. This dose allowed awakening 18 ± 9 hours later and time to extubation was 31 ± 16 hrs. There were no neurological sequelae. Although randomization was not attempted, 10 previous patients had 50% longer time to awakening and 40% longer time to extubation. Weaning required less powerful and lower doses of inotropes in the titrated dose patient.

Discussion: In addition to respiratory depression, high dose barbiturates for cerebral protection can depress the heart and circulatory system. These large doses are not titrated to a definable endpoint. We feel our end point at the time of hypothermia ensures complete cerebral protection as provided by barbiturates but with lower doses.

Conclusion: With EEG guided barbiturate dosing, awakening and extubation times are decreased. This method is physiologically precise because it utilizes the EEG to titrate barbiturate dosing with hypothermia thereby allowing lower barbiturate doses to insure cerebral protection.

Table 1. Demographics (N=14)

Age (Yrs)	57 ±13
Operative time (Min)	350 ± 6
Duration of bypass (Min)	168 ±26
Time of circulatory arrest (Min)	18.4 ± 5.1
Circulatory arrest temp (°C)	18.5 ± 1.3
Mean thiopental dose (mg/Kg)	18.2
Average time to awakening (Hrs)	18 ± 9
Average time to extubation (Hrs)	31 ±16

S115

Title: THE EFFECT OF ISOPROTERENOL ON MYOCARDIAL ISCHEMIA USING IMPEDANCE AS AN INDICATOR

Authors: M.B. Howie, MD, V.A. Romanelli, MD, T.D. McSweeney, BS, D.M. Vigder, BA, B.A. Byrne, BS.

Affiliation: Department of Anesthesiology, The Ohio State University Hospitals, Columbus, Ohio 43210

Introduction: Changes in tissue impedance have been shown to correlate with the onset and progression of ischemia in various tissues. Myocardial impedance has the potential to be a sensitive indicator of myocardial damage secondary to ischemia. Certain drugs may lead to a more rapid onset of ischemic tissue damage due to their enhanced effect on myocardial metabolism. Using frequency ranging impedance as a monitor, the increased rate at which myocardial tissue becomes ischemic can be observed. The purpose of this investigation is to note the effect of isoproterenol on dogs with acutely occluded coronary arteries (LAD). In addition, we further evaluated the efficacy of measuring myocardial impedance utilizing two standard ventricular pacing electrodes, a technique which may have specific application to open heart surgery.

Methods: After institutional approval, 12 dogs were anesthetized with chloralose, intubated, ventilated, and had arterial and pulmonary artery catheters placed. Median sternotomy was performed to facilitate myocardial exposure. All dogs were anticoagulated with heparin. The LAD was isolated in a distal position so that a discrete area of the left ventricle would be rendered ischemic upon LAD occlusion. Impedance was measured by using an AC current at a frequency of 1600 Hz through two standard ventricular pacing leads placed in the ischemic region distal to the LAD ligature. Impedance was then measured for 15 minutes (baseline). Using an infusion pump, isoproterenol was administered to the dogs at a rate of 15 ug/min. The LAD on each dog was occluded with a ligature (clamped) for a period of 60 minutes or until there was a 20% increase from baseline impedance. The ligature was then released (unclamped) allowing reperfusion. After the impedance stabilized or after 15 minutes, the isoproterenol infusion given to the study dogs was stopped. Impedance was then measured for 20 minutes after stabilization. HR, MAP, SAP, DAP, mean PAP, PSAP, PDAP and CO were recorded every 5 minutes and blood gas information every 15 minutes during the entire procedure.

Results: The characteristic response of impedance to LAD occlusion is shown for the non-treated dogs in Fig. 1 and for dogs given isoproterenol in Fig 2. The average time required for a 20% increase in impedance for the non-treated dogs was 48 ± 8 minutes. The average time required for dogs given isoproterenol was 10 ± 2 minutes. This 20% rise was significantly ($P<0.01$) shorter for the isoproterenol dogs. Upon administration of isoproterenol the heart rate rose to an average of 176 ± 23 until the isoproterenol was discontinued compared to an average heart rate of 134 ± 21 in non-treated dogs ($P<0.03$). Hemodynamic changes were observed in the reperfusion interval secondary only to ventricular arrhythmias.

Conclusion: The impedance response to ischemia is secondary to metabolic and ultrastructural cellular changes in the myocardium. Using impedance as a sensitive indicator of myocardial ischemia we have demonstrated that isoproterenol dramatically increases the rate at which the tissue becomes ischemic. Administration of isoproterenol especially in a period of myocardial stress should be done with extreme caution and very definite indications.

Figure 1:

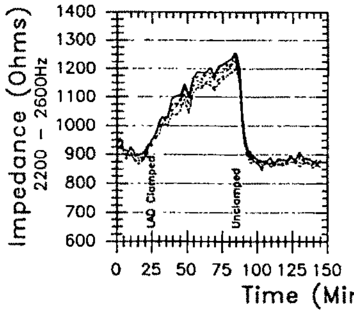
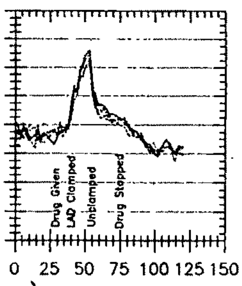


Figure 2:



S116

TITLE: **INTRAOPERATIVE COMPLICATION RATES DURING ELECTIVE AND EMERGENCY PROCEDURES**

AUTHORS: JC Hudson, M.D., C Gennings, Ph.D.*, FR Kane, Ph.D., BL Tyler, RN, RL Keenan, M.D.
AFFILIATION: Dept. of Anesthesiology & Biostatistics*, MCV, VCU, Richmond, VA 23298

Data from 63,393 cases (1984-1989) from a 1,000 bed Level 1 trauma hospital were entered into a Digital VAX-750 data base. Intraoperative complications (IOC) were categorized: Cardiac (C), Respiratory (R), Metabolic (M) and Other (O). Previous analysis (logistic regression) has shown that increasing ASA is associated with an increase in C, M, R and O ($p < 0.001$) and that emergency (Em) status ($p < 0.002$) is associated with increased rates in C, M, and O, but not in R (Ref). Here we show the individual IOC for elective (El) and Em within each category. The rank order of 36 IOC was established. Em has increased rates and a different rank order. (Table 1) The influence of ASA upon selected IOC is displayed (Table 2). Hypotension, hypertension and hypothermia are consistently the leading problems.

Discussion: The increase in hemorrhage (Em/El 6.77), asystole (4.82), aspiration (3.82), hypoxia (3.82) tachycardia (3.33), hypercarbia (2.68) and oliguria (2.33) are consistent with hypovolemia and trauma related injury. A shift in population in Em to higher ASA also contributes to higher Em rates. (I & II 58.48%→45.92%, III & IV 41.44%→48.35%)

Reference: Anesthesia and Analgesia 70:S166, 1989.

Table 1 INTEAOPERATIVE COMPLICATION RATES (%)

	Elective n=55141		Emergency n=8252		Overall n=63,393	Em/El
	Rank	%	Rank	%	%	
Hypotension	1	4.97	1	8.98	5.49	1.81
Hypertension	2	4.49	3	3.83	4.40	0.85
Temp <35°	3	3.32	2	5.16	3.53	1.55
Diff Intub	4	2.90	8	1.82	2.76	0.63
Bradycardia	5	2.27	7	1.94	2.22	0.85
Tachycardia	6	1.61	4	3.66	1.87	3.33
V. ectopy	7	1.53	9	1.82	1.57	1.19
Oliguria	8	1.45	5	3.38	1.70	2.33
Diff airway	9	1.43	14	1.11	1.39	0.78
Laryngospasm	10	1.19	25	0.46	1.09	0.39
Bronchospasm	11	0.71	19	0.76	0.72	1.07
Lytes Abn	18	0.34	6	1.96	0.57	5.70
Hypoxemia	25	0.28	16	1.07	0.38	3.82
Hemorrhage	26	0.26	10	1.76	0.45	6.77
Hypercarbia	27	0.22	21	0.59	0.27	2.68
Asytole	32	0.11	23	0.53	0.16	4.82
Aspiration	35	0.03	31	0.13	0.04	4.33

Table 2 COMPLICATION RATES (Elective)

ASA	I	II	III	IV
Hypotension	0.97	3.19	7.52	12.24
Hypertension	0.71	3.50	6.85	8.17
Hypothermia	1.68	3.02	4.22	4.80
Diff Intub	1.45	3.28	3.43	2.08
Hypoxemia	0.07	0.20	0.35	0.82
Hypercarbia	0.16	0.16	0.20	0.71

S117

TITLE: Blood Coagulation is Delayed After Passage Through an Epidural Catheter

AUTHORS: H.K. Humphreys, M.D. and Brian R. Jones, M.D.

AFFILIATION: Department of Anesthesiology, University of California, Davis Medical Center

INTRODUCTION: Recently the technique of prophylactic epidural blood patch (PEBP) has been popularized to decrease the incidence of post-dural puncture headache (1). PEBP involves passing fresh, aseptic, autologous blood into the epidural space via an existing epidural catheter.

This study was designed to determine whether the coagulation profile of blood would be altered after passage of the blood through an epidural catheter.

METHODS: Approval from our IRB was obtained. Informed consent for venipuncture was obtained from 20 healthy adult volunteers. Seven milliliters of blood were obtained by antecubital venipuncture through a 21 gauge needle. The blood sample was then immediately analyzed for baseline coagulation by Sonoclot profile, activated clotting time (ACT) and platelet count. Thereafter a second sample of blood was obtained by repeat venipuncture, passed through an epidural catheter directly into cuvettes and promptly analyzed. Statistical analysis was performed by paired two-tailed t-test. All values are expressed as mean ± standard deviations (SD).

RESULTS: Sonoclot time to initial peak was delayed after passage through the catheter from 7.0 ± 1.6 to 8.8 ± 2.0 (min). ACT was also delayed from 110 ± 30 to 127 ± 9 (sec). Platelet count, however, remained unchanged after passing through the catheter, 263 ± 88 (baseline), 265 ± 82 (catheter) (1,000 per cm^3). The increases in Sonoclot and ACT values were statistically significant ($p < 0.01$).

DISCUSSION: Since platelet count remained unchanged after catheter passage, the coagulation delays may be due to impaired platelet function rather than decreased number of platelets. A recent study by Cook et al showed that blood mixed with cerebral spinal fluid has a rapid coagulation response (2). It is possible that this rapid *in vivo* response would overwhelm the small coagulation delays that we observed *in vitro*.

In conclusion, while our data show a statistically significant slowing of coagulation after passage of the blood through an epidural catheter, it seems unlikely that these small delays have clinical significance, and probably should not effect the clinician's decision to give a blood patch prophylactically.

Table 1: Coagulation Parameters (Mean ± S.D.)

	Baseline	After Catheter Passage
*Sonoclot (min) n = 20	7.0 ± 1.6	8.8 ± 2.0
*ACT (sec) n = 16	110 ± 30	127 ± 9
Platelets x 1,000 n = 7	263 ± 88	266 ± 82

*P < .005

REFERENCES
1. Colonna-Romano P, Shapiro BE. Unintentional dural puncture and prophylactic epidural blood patch in obstetrics. Anesth Analg 69:522-3, 1989.
2. Cook MA, Watkins-Pitchford JM. Epidural blood patch: a rapid coagulation response [letter]. Anesth Analg 70:567-8, 1990.

S118

TITLE: COMPARISON OF INTRAOPERATIVE WARMING DEVICES

Authors: JM Hynson M.D., DI Sessler M.D.

Affiliation: Department of Anesthesia, UCSF, San Francisco, CA 94143

Mild hypothermia remains an almost inevitable consequence of anesthesia and surgery. We therefore evaluated the efficacy of three intraoperative warming techniques.

With IRB approval, 12 patients undergoing kidney transplantation were randomly assigned to: 1) a full length (54 X 145 cm) circulating water blanket set at 40°C positioned under the subject (N=4); 2) humidification and heating to 40°C of inspired gases (N=3); 3) skin surface warming of the lower extremities (to mid thigh level), using a Bair Hugger® convective air warmer set on "high" (≈43°C) (N=4); and 4) no extra warming (control) (N=5). Intravenous fluids were warmed in all groups. Fresh gas flows were maintained at 5 L/min without a heat and moisture exchanger. Ambient temperature and preoperative conditions were similar in all groups. Tympanic membrane temperature was measured starting 30 min before induction of anesthesia.

In all groups, tympanic membrane temperature decreased ≈0.7°C, during the first 30 min (fig.). Tympanic membrane temperatures in patients given forced air warming began to increase ≈60 min after induction. Those given external warming with the circulating water blanket, had little further decrease in temperature after the first h of anesthesia. Central temperatures continued to decrease throughout the 3 h study period in the control and heated humidifier groups.

We conclude that convective air warming of the legs is more effective than the use of a circulating water blanket. Heated humidification offers little protection from intraoperative hypothermia.

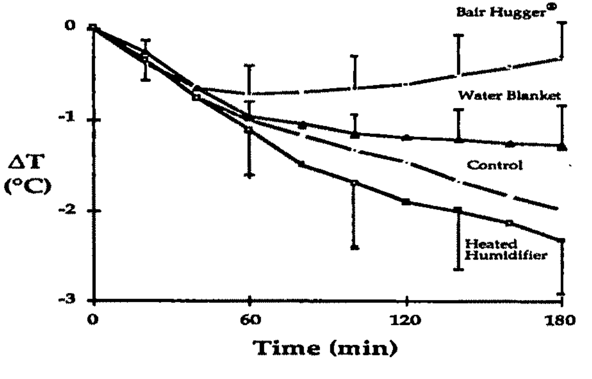


Figure. After initially decreasing, central temperature began to increase in patients given convective air warming. Error bars in the control group were deleted for clarity, but were similar to those in the other groups.

Supported by National Institutes of Health grant #R29 GM39723.

S119

TITLE: ABSENCE OF NONSHIVERING THERMOGENESIS IN ANESTHETIZED ADULTS

Authors: JM Hynson MD, DI Sessler MD, A Moayeri BS, J McGuire
Affiliation: Department of Anesthesia, UCSF, San Francisco, CA 94143

Nonshivering thermogenesis, an important thermoregulatory mechanism in animals and newborn humans,[1] is defined as an increase in metabolic heat production in response to hypothermia. We have previously shown that thermoregulatory vasoconstriction is preserved during general anesthesia, but triggered at central temperatures ≈2.5°C below normal.[2] We therefore tested the hypothesis that an increase in oxygen consumption, associated with nonshivering heat production, occurs in response to moderate hypothermia in anesthetized adults.

Following IRB approval, anesthesia was induced in four volunteers by inhalation of isoflurane and N_2O (70%). Vecuronium was used for neuromuscular paralysis. Anesthesia was maintained with ≈1.1% isoflurane in air. Volunteers were maintained normothermic for 45 min and then actively cooled using circulating water blankets set at 5°C. Thermoregulatory vasoconstriction was prospectively defined as a forearm - fingertip gradient ≥4°C.[3] Each volunteer was cooled to a central temperature at least 1.0°C below the temperature at which thermoregulatory vasoconstriction was first detected. Oxygen consumption was calculated from minute ventilation and inspired and mixed expired concentrations, measured with a mass spectrometer.[4]

Thermoregulatory vasoconstriction occured at 35.5±0.5 (SD) °C. Oxygen consumption decreased ≈7%/°C which is in agreement with previously published data.[5] Despite forcing central temperature 1°C below the vasoconstriction threshold, there was no increase in oxygen consumption (fig.).

We conclude that nonshivering thermogenesis is not an important source of heat production in anesthetized adults.

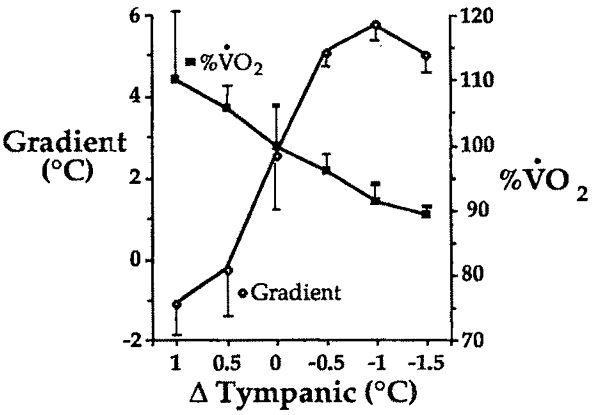


Figure. Oxygen consumption as a percentage of oxygen consumption at time of vasoconstriction. Temperature is shown as a change from the temperature at the threshold for vasoconstriction.

References:

1. Sinclair JC, Temperature Regulation and Energy Metabolism in the Newborn (pp 157-185). Grune & Stratton, New York, NY, 1978.
2. Sessler DI, et al, Ansthesiology 68:836-842, 1988
3. Sessler DI, et al, Anesth Analg 70:S363, 1990
4. Orkin FK, Cooperman LH. Complications in Anesthesiology (p 626). J.B. Lippincott, Philadelphia, PA, 1983.

Supported by National Institutes of Health grant #R29 GM39723.

S120

RELATIONSHIP BETWEEN ANTITHROMBIN III-HEPARIN COMPLEX AND ACTIVATED CLOTTING TIME IN CARDIAC SURGERY

AUTHORS: E. Inada, MD, K. Aoki, MD, H. Aoki, MS, M. Kohama, MD, S. Takanashi, MD, K. Iwahashi, MD, S. Furuta, MD
AFFILIATION: Anes. Dept. Mass. Gen. Hosp., Boston, MA 02114, and Surg. Dept., Cardiovasc. Inst. Hosp., Tokyo

Activated clotting time (ACT) is affected by a variety of factors including plasma levels of heparin (H), antithrombin III (AT III)-heparin complex (AHC), blood temperature (BT), and other factors, but a quantitative relationship has not been demonstrated. We undertook this study to reveal the dose-relationship among H dose, ACT, AT III, AHC, and BT.

Nine adult patients undergoing cardiac surgery were studied. Informed consent was obtained with institutional approval. The following parameters were measured: ACT, BT, and plasma levels of H, AT III, and AHC. ACT was measured by Hemochron^{TM}. Plasma levels of H, AT III, and AHC were measured by chromogenic assays. H was given in increments of 50 U/kg, 100 U/kg, and again 100 U/kg, for a total of 250 U/kg, 5 mins. apart before cardiopulmonary bypass (CPB). The priming solution contained 125 U/kg of H. Measuring points were: A) before H IV, B) 3 mins. after the first dose of H, C) 3 mins. after 2nd dose of H, D) 3 mins. after 3rd dose of H, E) 8 mins. after 3rd dose of H, and F) 30 mins. after the initiation of CPB. Data were analyzed by t-test, ANOVA and multiple linear regression analysis. A p value of < 0.05 was considered to be significant.

Table 1 shows the results. The relationship between ACT (sec), plasma levels of AHC (U/ml), and BT (°C) was approximated by the formula: ACT=250.0*AHC-3.2*BT+1821.6 (R^2 =0.76).

During hypothermic CPB, ACT was pro longed while plasma AHC and H levels were decreased and, AT III activity was decreased by half. We conclude that there is a predictable relationship between ACT and plasma AHC levels and BT.

Table.1

	ACT (sec)	Heparin (units/ml)	AHC (units/ml)	AT III (%)	BT (℃)	aPTT (sec)
A	150 = 10	<0.01	<0.01	78.3 ± 9.3	35.5± 0.6	44.7± 7.2
B	259 = 29 •	0.66± 0.14	0.46± 0.08	79.8 ± 11.8	35.0± 0.7	341 ± 56.7 •
C	409 = 55 •	2.45± 0.47 •	0.72± 0.14 •	79.8 ± 9.4	34.9± 0.7	>400
D	510 = 95 *	3.71± 0.69 ″	1.13± 0.26 *	82.6 ± 13.7	34.9± 0.7	>400
E	505 = 94	3.57± 0.68	1.13± 0.28	81.4 ± 12.6	34.9± 0.7	>400
F	733 = 243″	2.77± 0.33 •	0.52± 0.13 •	43.2 ± 6.5 •	26.2± 1.8•	>400

ACT=activated clotting time, AHC=antithrombin III-heparin complex, aPTT=activated partial thromboplastin time, • =p<0.001 ,* =p<0.01, and ″ =p<0.05 compared with the previous value

S121

TITLE : PLATELET AGGREGATION AND FIBRINOLYTIC ACTIVITY DURING CARDIOPULMONARY BY-PASS.

AUTHORS : C. ISETTA MD., C. ROUL MD., C. SAMAT MD.,
M. KOTAICHE MD., J. JOURDAN MD.
AFFILIATION : DEPARTMENTS OF ANESTHESIOLOGY-CRITICAL CARE,
HAEMATOLOGY LABORATORY AND CARDIAC SURGERY.
CENTRE HOSPITALIER UNIVERSITAIRE, NICE 06000 FRANCE.

INTRODUCTION : It is well know that during cardiopulmonary by-pass (CPB) the coagulation cascade is activated (1). Nevertheless few studies are focused on fibrinolysis and platelets during CPB with a fibre oxygenator. The aim of this study is to observe the platelet aggregation and to measure the fibrinolytic activity during and after CPB.

METHODS : After following Institutional Review Board approval and informed consent, ten patients undergoing cardiac surgery were investigated. In the immediate preoperative period, two patients were treated by acetyl salicylic acid (ASA). The CPB including a hollow fibre oxygenator (Capiox E, Terumo) was primed with a 3,5 % dextran 40,000 (Plasmacair, Synthelabo). Anticoagulation was performed by a single administration of heparin (300 Units/kg) before the initiation of CPB. During CPB, non-pulsatile flow kept above 2 l/min/m2 and moderate hypothermia were employed. Seven blood samples were drawn on the arterial line, T1 : after induction of anesthesia, T2 : 15 min, T3: 30 min, T4 : 45 min after onset of CPB, T5 : at the end of CPB, T6: 90 min after the end of CPB, T7 the morning of the first postoperative day. At each time the platelet aggregation (Photometer PAP 4 Biodata) was studied. The data of platelet aggregation (BTG, PF4) and fibrinolytic activity (fibrinogen, D-dimere, t-PA, PAI, CFC) and platelet number, hematocrit (HT), ACT, PT were measured.

RESULTS : For 8 patients the platelet aggregation was normal before the CPB, it was increased since the first 15 min and became again normal on the first postoperative day. For the 2 patients on ASA, there was a platelet hypoaggregation before CPB, but during and after CPB a normal aggregation was observed. The data are reported on the table. At each time the CFC research was always negative.

DISCUSSION : The fibrinolytic system activation was the sign of a significant inflammatory syndrom wich started before the CPB. There was no correlation between the BTG and PF4 levels and the platelet aggregation intensity. There was no clinical fibrinolytic activity. The aggregation data suggest that patient blood contact with foreign surfaces during CPB resulted in platelet hyperaggregation wich can reverse the platelet hypoaggregation ASA induced.

REFERENCE : (1) Blood Purif, 5 : 168-178, 1987

n=10	PLATELETS (10.6/L)	B TG (UI/L) (5-15)	PF4 (UI/ ML) (5-15)	PT (%)	HT (%)
T1	255±73	167±37	97±20	91±8	38±3
T2	186±69	155±44	77±28	34±5	28±3
T3	198±80	150±60	85±30	35±5	29±2
T4	196±64	187±20	91±62	33±9	29±3
T5	178±37	178±15	93±46	40±7	27±3
T6	198±61	165±28	110±26	72±9	32±4
T7	221±73	161±45	92±20	83±11	35±4

n=10	FIBRINOGEN (G/L)	t-PA (UI/L) (0.3-0.5)	PAI (UI/ML) (5-8)	D-DIMERE(ug/L) (<0.5)	ACT (sec) (28-32)
T1	3.9±1.0	1.4±1.5	15.6±13.2	2.2±1.2	42±16
T2	2.5±0.7	3.4±4.1	18.1±18.2	3.7±3.1	>120
T3	2.7±0.4	1.8±1.3	13.6±12.0	3.7±3.1	>120
T4	2.8±0.7	1.4±1.1	16.0±10.3	5.2±3;4	>120
T5	2.5±0.7	2.1±1.7	25.6±24.5	6.2±3;5	>120
T6	2.9±0.9	1.1±1.0	30.8±18.5	6.2±3.5	46±11
T7	4.7±1.1	1.3±1.1	19.0±14.4	6.8±2.7	40±8

TABLE : MEAN VALUES ± SD

S122

TITLE: CONTROLLED COMPARISON OF THE ANTI-EMETIC EFFICACY OF THIETHYLPERAZINE AND DROPERIDOL IN OUTPATIENT SURGERY

AUTHORS: B.R. Jacobs, M.D., T.Z. O'Connor, M.P.H.
AFFILIATION: Anes. Dept., Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

Introduction: Postoperative nausea (N) and vomiting (V) commonly delay discharge from the recovery room (RR). The increasing number of outpatient surgical procedures requires improved RR efficiency. We compared thiethylperazine (Norzine), a phenothiazine, and droperidol (Inapsine), a butyrophenone, to placebo when administered intraoperatively. Although thiethylperazine has been commercially available since the 1960's, no study has evaluated its antiemetic efficacy in outpatient surgery. Parameters evaluated were postoperative N and V, sedation, and times to oral intake (po's), ambulation and discharge.

Methods: Following IRB approval and written informed consent, 22 patients (8 droperidol, 7 thiethylperazine, 7 placebo) undergoing gynecologic laparoscopic surgery with general endotracheal anesthesia were evaluated. Each patient received a standardized combination of midazolam, fentanyl, sodium thiopental, and vecuronium intravenously. Maintenance was achieved with 70% nitrous oxide in oxygen and end tidal isoflurane concentrations 0.25-2.0%. Patients received single doses of either thiethylperazine 10 mg IM, droperidol 1.25 mg IV, or placebo (normal saline) within 10 min after intubation in this double-dummy, randomized, parallel group trial. No other antiemetic agents were administered pre- or intraoperatively. An orogastric tube was inserted intraoperatively and maintained in place until just prior to extubation. N and sedation were evaluated postoperatively in the RR at half-hourly intervals until discharge using a categoric scale of (0-3). V was evaluated continuously and quantified as the number of episodes (including retching) reported. The times from RR admission to 1) po's, 2) ambulation, and 3) discharge were recorded. The analysis for demographics, times to orals, ambulation, and discharge were done by ANOVA, with chi-square analysis being used for comparisons of N, V, and sedation.

Results: Demographics were similar between groups. Compared with placebo, thiethylperazine significantly decreased the time to po's ($p<0.05$) and the incidence of N ($p<0.001$) without increasing sedation (p=ns). Droperidol also decreased the incidence of N ($p<0.01$) while causing an increased level of sedation ($p<0.03$) compared with placebo. Droperidol did not differ from placebo in time to po's. When comparing thiethylperazine with droperidol, there were no significant differences between either group for any of the variables tested. In addition, there were no significant differences between each of the groups for time to ambulation or the incidence of V. Times to discharge for thiethylperazine, droperidol, and placebo were 135, 142, and 181 min, respectively, which were not significantly different. No adverse reactions were reported.

Discussion: Both thiethylperazine and droperidol significantly decreased the incidence of N postoperatively. Thiethylperazine also significantly decreased the time to po's without increasing sedation. In this study, a single IM dose of thiethylperazine compared favorably with droperidol. Both drugs decreased the incidence of postoperative N and allow for more efficient RR turnover with an average discharge time of 40 min faster than that of placebo. These pilot results support earlier findings that thiethylperazine is a safe and effective antiemetic that causes minimal sedation, making it desirable for use in outpatient surgery.

S123

TITLE: THE COMBINATION OF INTRATHECAL MORPHINE AND PCA PROVIDES EXCELLENT POSTOPERATIVE ANALGESIA.

AUTHORS: L.Jacobson,MD, C.Chabal,MD. A.Mariano,PhD. E.Chaney,PhD
AFFILIATION: VAMC, Univ.of Washington, Seattle, WA 98108

Introduction: Intrathecal morphine (ITMS) provides profound and prolonged postoperative analgesia of gradual onset and regression. When the effects of ITMS recede patients may experience severe discomfort. Intravenous Patient Controlled Analgesia (PCA) enables patients to self administer opioids to fulfil their own unique requirements. However, unless patients are given sufficient opioid prior to commencing PCA, the transition through the regression of anesthesia to the establishment of satisfactory postoperative analgesia can be protracted and painful. The combination of ITMS and PCA may facilitate this transition.

Methods: After obtaining Institutional Review Board approval, the Acute Pain Service records and charts of 92 patients who had undergone either total hip (THR;n=43) or total knee (TKR;n=49) replacement surgery were reviewed. They were divided into 2 groups (PCA;n=47 & ITMS+PCA;n=45) according to the type of postoperative analgesia they received. The choice of anesthesia and mode of postoperative analgesia was at the Anesthesiologists discretion. PCA (initial dose 1 mg.; dose interval 8 min.) was attached to all the patients on the PARU upon arrival from the operating room. In the ITMS group 0.5mg preservative free morphine was administered at the time of induction of anesthesia. Information on the duration of analgesia (time to the initial use of PCA) and the quantity of morphine used in the 24 hour period from the induction of anesthesia (efficacy) was obtained from a printer connected to the PCA machine. Adverse effects such as pruritus, nausea, vomiting, clinical respiratory depression, excessive drowsiness and urinary retention were assessed. Statistical analyses were performed using Students T Test and the Chi Square Test. $P<0.05$ was considered statistically significant.

Results: The average time to the initial demand for intravenous morphine from the PCA was more prolonged with ITMS+PCA (14h) than with PCA alone (6h); $P<0.001$. The amount of intravenous PCA morphine used in 24h was less following ITMS+PCA (7mg) than PCA (28mg); $P<0.001$. Pruritus and urinary retention requiring catheterization were statistically more common following ITMS+PCA than PCA. Nausea and vomiting were equally distributed between the groups. Clinical respiratory depression and excessive drowsiness were not encountered.

Discussion: In the patients surveyed the combination of ITMS+PCA was an effective, safe and practical method of delivering postoperative analgesia. The ITMS+PCA and PCA groups differed in duration and efficacy of analgesia. In this case series other factors, such as intraoperative opioid administration and the choice of anesthesia, could have entered into the differences between the groups. Nevertheless the magnitude of the difference is such that further controlled investigations are warranted. The goal of effecting a smooth transition to satisfactory postoperative analgesia was achieved with ITMS+PCA. ITMS+PCA is a rational approach to a problem commonly encountered in postoperative pain management.

S124

TITLE: INTRATHECAL FENTANYL IN THE EVALUATION OF PERSISTENT LOW BACK PAIN

AUTHORS: L.Jacobson,MD, C.Chabal,MD, A.Mariano,PhD.,E.Chaney,PhD

AFFILIATION: VAMC, Univ of Washington, Seattle,WA 98108.

Introduction: Intrathecal fentanyl could be useful in the evaluation of persistent low back pain (LBP) because it produces a selective block of pain without the sensory and motor effects associated with intrathecal local anesthetic; the conventional method of diagnostic spinal injection.

Methods: After obtaining Institutional Review Board approval, and written informed consent, 18 patients with persistent LBP were studied using a randomized, placebo controlled, and double blinded crossover design. The patients each received 3 separate lumbar intrathecal injections at least 1 week apart; 1) CSF 1.4 ml. aspirated and reinjected. 2) Fentanyl (F) 25 mcg (0.5 ml) made up to 1.4 ml. with CSF. 3) Lidocaine 5% (L) 70 mg. (1.4 ml) Assessments were performed preinjection (baseline),and at 5, 10, 15, 30 minutes, 1, 2, 3 and 4 hours postinjection. Pain was assessed by verbal patient response using a numerical pain rating system; 0 = no pain to 10 = worst pain imaginable. Duration of analgesia, sensation of warmth and adverse effects were noted. If satisfactory analgesia was still present at the time of discharge the patients were requested to note when the pain returned. After the final injection patients were asked which of the 3 treatments was best. Statistical analyses were performed using the Friedman Test, Wilcoxon's test and the Chi Square test. $P< 0.05$ was considered statistically significant.

Results: The average age was 57 years with a median LBP duration of 20 years. There was no marked difference in the baseline median pain scores between the groups; $P>0.05$: CSF = 4; F = 6; L = 5: The baseline and best CSF pain scores were different;$P=0.05$. The best pain scores (median) (CSF = 3; F = 0; L = 0) were much better for F and L relative to their own baseline levels as well as when compared to the best CSF scores; $P<0.001$. The median duration of analgesia (hours) (CSF = 0; F = 12; L = 3) was significantly longer with both F and L than with CSF; $P<0.001$. F provided more prolonged analgesia than L. Unique effects of F included pruritus 16(89%) and a sensation of warmth affecting the trunk and lower limbs; 10(56%). Motor and sensory paralysis was confined to the L group. Fentanyl was considered the best drug by the majority of patients; 11(61%).

Discussion: Despite a placebo component, both F and L were superior and neither differed from each other. Physicians who administer diagnostic spinal injections for the evaluation of persistent LBP may find fentanyl useful because the sensory and motor cues associated with lidocaine are absent. Intrathecal fentanyl was, however, associated with itching and warmth, cues which could influence the patients interpretation of its effects.

S125

TITLE: NEEDLE POSITION FOR PARAVERTEBRAL AND SYMPATHETIC NERVE BLOCKS: RADIOLOGIC CONFIRMATION IS NEEDED

AUTHORS: S Jain, MD, N Shah, MD, R Bedford, MD
AFFILIATION: Memorial Sloan-Kettering and Cornell Univ. Med College, NY, NY

INTRODUCTION: Paravertebral and sympathetic nerve blocks are most often performed using anatomical landmarks, albeit not always successfully. During the past 3 years we have uniformly utilized X-ray confirmation of needle position during these procedures. A summary of this experience affords some observations regarding causes for unsuccessful blocks occurring when only anatomic landmarks are utilized for needle positioning.

METHODS: 375 consenting patients underwent 65 lumbar sympathetic blocks and 310 paravertebral blocks. Needles were placed strictly according to anatomical landmarks, as previously described.[1] After the first needle pass, the location of the needle tip was confirmed with injection of 2 ml of radiopaque dye; fluoroscopy or CT scan was then performed and the needle tip position was recorded. If redirection of the needle was required, the block was performed only after confirming correct position with one or more subsequent radiologic exams.

RESULTS: Correct needle placement on the first attempt (based on anatomical landmarks) occurred in 67% of paravertebral blocks and 78% of lumbar sympathetic blocks.The difference was not significant. The incorrect needle placements for both blocks are summarized in the following table:

Needle Tip Location	# Incorrect	Incidence
Too superficial or Lateral	63	17%
Epidural or Paravertebral	20	5%
Too Deep	15	4%
Too Medial	9	2%

DISCUSSION: These data confirm that strict reliance on anatomic landmarks for performing paravertebral and lumbar sympathetic blocks is not reliable for accurate needle localization and reliable results. This has particularly serious consequences should a neurolytic procedure be contemplated. We conclude that radiologic confirmation is necessary to obtain predictable results from both paravertebral and lumbar sympathetic blocks.

REFERENCE: Moore DC: Regional Block. 4th ed. Springfield, Illinois, Charles C. Thomas, 200-210.

S126

INTRAOPERATIVE ISCHEMIA: COMPARED TO WHAT?

U Jain MD PhD, TLK Rao MD, A Krishnamurthy BS, DE Wallis MD, JF Moran MD
Loyola Univ. Med. Center, Maywood, IL 60153

INTRODUCTION: Because of the high incidence of persistent electrocardiographic (ECG) abnormalities, to determine intraoperative ischemia, it is customary to compare the ECG at the time of interest to a baseline ECG to determine acute changes. The ECG obtained the night before surgery has been used as the baseline.[1] This is not very suitable because changes in electrode positions[2] and use of different electrocardiographs can lead to significant changes in the ECG. Additionally, the patient may have been ischemic when this ECG was recorded. The ECG obtained on arrival in the operating room, prior to anesthetic induction, has been widely used as the baseline.[3] To evaluate this, the ECGs on arrival were compared with the ECGs after anesthetic induction, but prior to incision.

METHODS: After Institutional Review Board approval, written informed consent was obtained from 103 aortocoronary bypass surgery patients to record ECG leads I, II, III, AVR, AVL, AVF, and V_5, in accordance with the American Heart Association guidelines. Only the differences in ST segment values between ECGs on arrival and prior to incision were analyzed. The ECG with greater ST deviation was considered to be ischemic if there was at least a 1mm downsloping or horizontal ST depression, or a 2mm upsloping ST depression, or a 1mm ST elevation in a non-Q wave lead.[3]

RESULTS: The ECG on arrival was more ischemic in 6 patients on the basis of downsloping or horizontal ST depression, in one patient on the basis of upsloping ST depression, and in one patient on the basis of ST elevation in a non-Q wave lead; thus, a total of eight patients. The ECG prior to incision was more ischemic in 2, 0, 0, 2 patients, respectively.

DISCUSSION: If the ECG on arrival is considered as the baseline,[3] only 2 patients would be considered to have a change in ischemia while ignoring 8 other patients. Baseline can be determined only if continuous or multiple frequent ECG recordings over several hours are available. During this period, the patient position, electrode positions, and the electrocardiograph should not change, and there should be no stimulation. Such recordings are usually not available. If necessary, amongst the available ECGs, the one with the least ST deviation may be considered to be the baseline.

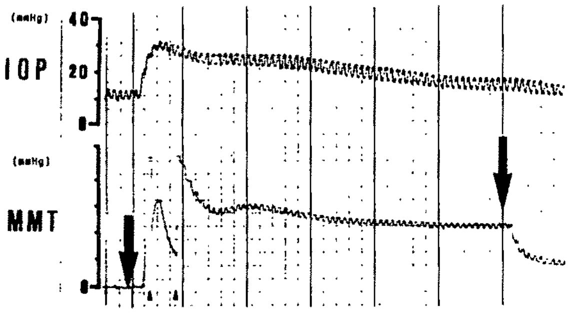
REFERENCES: (1) Slogoff et al. Anesthesiology 62:107-114, 1985; (2) Rantaharju et al. J Electrocardiol 13:109-114, 1980; (3) Cheng et al. Anesthesiology 71:818-826, 1989.

S127

Title: PORCINE "MASSETER SPASM" IS NO SPASM
Author: J-P Jantzen, MD,DEAA; HJ Hennes, MD; AM Klein, MD; O Kempski, MD*
Affil.: Departments of Anaesthesiology and Neurosurgical Pathophysiology*, J Gutenberg University Med.School Mainz, FRG

The administration of succinylcholine (SCH) to humans or pigs susceptible to malignant hyperthermia (MHS) results in an increase in masticatory muscle tone (1, 2). This hitherto ill defined phenomenon is refered to as "masseter spasm" (MS)(3). We have attempted to elucidate the pathophysiology of MS in a porcine model.

With approval of the protocol by the state authority, 5 MHS pigs were anesthetized (piritramide/ pancuronium) and instrumented. Intraocular pressure (IOP) was measured manometrically in the anterior chamber; masticatory muscle tone (MMT) was assesed with a intermolar balloon that was connected to a pressure transducer and calibrated to zero prior to SCH administration.



Effects of SCH (1st marker) and dantrolene (2nd marker) on IOP and MMT (paper speed 0,5 mm/sec)

Despite complete neuromuscular blockade (NB; monitored with EMG) SCH (1,5 mg/kg) produced an increase in MMT in all pigs which was reversed by dantrolene (0,5 mg/kg·min)(fig). The time course of MMT paralleled that of the IOP, suggesting a similar underlying mechanism.

SCH increases extraocular muscle tone (4); the resulting IOP increase is not prevented by NB (5).

We speculate that the increases in MMT and IOP reflect the same process, i.e. a SCH-induced stimulation of intramyocellular contractile filaments that is independent of neuromuscular transmission. Hence, according to physiological terminology, MS is a *contracture*, not a *spasm*.

REFERENCES:

1. Van der Spek AFL et al. (1988) Anesthesiology 69:11
2. Leiman BC et al. (1988) Anesthesiology 69 :A412
3. Schwartz L et al. (1984) Anesthesiology 61 : 772
4. Lincoff HA et al. (1957) Am J Ophthalmol 43 : 440
5. Meyers EF et al. (1978) Anesthesiology 48 : 149

S128

Title: DROPERIDOL BLOCKS EPHEDRINE INDUCED INCREASES IN RENAL BLOOD FLOW IN HALOTHANE ANESTHETIZED DOGS
Author: P-O Jarnberg, M.D., Ph.D., L.L. Priano, M.D., Ph.D.
Affiliation: Dept. of Anesth., Oregon Health Sciences Univ., Portland, OR 97201

Introduction: Recently ephedrine was reported to increase renal plasma flow and urine output in humans after abdominal aortic surgery[1] resembling the effects of dopamine on renal function.[2] To evaluate if ephedrine's renal effects are mediated via dopamine receptors we decided to study its effects in dogs with and without blockage of dopamine receptors.

Methods: Sixteen male mongrel dogs weighing 17-28kg were studied after institutional approval. The dogs were randomly assigned to receive either ephedrine (E) or droperidol followed by ephedrine (DE). Anesthesia was induced with thiopental 10mg/kg IV and maintained with halothane 2% in N_2O/O_2, 50/50. The animals were ventilated to normocarbia. Thermodilution pulmonary arterial, right atrial and descending aortic catheters were inserted via cutdowns. The right renal artery was exposed via a laparotomy and an electromagnetic flow probe positioned snugly around it. The urinary bladder was catheterized. Normal saline was infused at 10ml/kg/h via a peripheral vein. RBF was allowed to stabilize after surgery. The bladder was emptied and urine collected for a 30 min. control period. At the midpoint of this control time, CO was determined and blood samples obtained for sodium and ABG determinations. After the control period, E-dogs received ephedrine 10 μg/kg as a bolus followed by an infusion of ephedrine at 2 μg/kg/min for another 30 min while DE-dogs received droperidol 0.2mg/kg IV followed after 60 min by ephedrine as above. Urine collection, blood sampling and CO determinations were repeated as during control.

Results: Ephedrine increased RBF, urine flow rate (UF) and urinary sodium excretion (C_{Na}) by 29%, 153% and 296% respectively. These increases were totally abolished after pretreatment with droperidol.

mean±SEM	RBF ml/min	UF ml/min	C_{Na} ml/min	MAP mmHg	CO l/min
Control	176±19	0.84±0.20	0.51±0.13	80±4	2.8±0.2
E	228±25[b]	2.04±0.36	2.02±0.38[c]	95±5[b]	3.8±0.2[b]
Control	156±20	0.80±0.15	0.58±0.17	83±5	2.5±0.3
DE	157±22	0.65±0.09	0.63±0.14	75±3	3.1±0.2[a]

a-$p<0.05$ vs control b-$p<0.01$ vs control c-$p<0.001$ vs control

Discussion: These data confirm that ephedrine increases RBF, UF and C_{Na}. Pretreatment with droperidol which is a known dopamine receptor blocker[3] abolished these effects indicating that ephedrine's renal effects may be mediated via dopamine receptor activation. We conclude that ephedrine as an infusion can be an alternate choice to dopamine for augmenting renal function under anesthesia.

References: 1. Acta Anesthesiol Scand 32:271, 1988. 2. Pharmacol Rev 24:1, 1972. 3. Br J Anaesth 52:879, 1980.

S129

Title: EFFECT OF INFILTRATION ANESTHESIA ON POSTTONSILLECTOMY PAIN

Authors: J A Jebeles, MD, J S Reilly, MD, J F Gutierrez, MD, E L Bradley, Jr, PhD, I Kissin, MD
Affiliation: University of Alabama School of Medicine, Birmingham, Alabama 35294

Postoperative pain management is a difficult problem in all patients, yet especially so in the pediatric age group. Sustained spinal cord hyperexcitability produced by massive nociceptive impulses could contribute to postoperative pain If formation of the sustained hyperexcitable state during surgery maintains postoperative pain, neural blockade with a local anesthetic could result in a decreased level of postoperative pain well beyond the duration of action of the local anesthetic used.

In a double-blind randomized study with informed consent and institutional approval, 14 patients between the ages of 8-16 years old scheduled for tonsillectomy with or without adenoidectomy were divided into two groups. All patients received 0.006 mg·kg^{-1} atropine and anesthesia was induced by inhalation of halothane. Atracurium 0.5 mg·kg^{-1} was used for myorelaxation. After oral intubation anesthesia was maintained with isoflurane and nitrous oxide/oxygen (2:1). In Group I, 5 minutes before incision the tonsillar fossae were infiltrated with 0.25% bupivacaine with epinephrine (1:200,000). In Group II, the tonsillar fossae were infiltrated with normal saline with epinephrine (1:200,000).

Postoperatively all patients were treated for pain identically. Morphine 0.07 mg·kg^{-1}, i.v. was given in the recovery room. All patients received oral elixir with codeine 0.05 mg·kg^{-1} and acetominophen 5 mg·kg^{-1} every 4 hours. Postoperative pain assessments were made using the visual analog self rating method. Two types of pain were assessed: constant incisional pain and pain caused by drinking 100 ml of water. The time required to swallow the water was also recorded. Eight assessments were made between four hours postoperatively and p.o.d. 10.

A significant difference was noted between the groups (Table). Of importance is the fact that the differences were present even at postoperative day 10, well beyond the duration of action of the local anesthetic used. An explanation for this longlasting pain relief might be that neural blockade prevents nociceptive impulses from entering the central nervous system during and immediately after surgery and thus suppresses formation of the sustained hyperexcitable state that is responsible for the maintenance of postoperative pain.

Table. Effect of bupivacaine on postoperative pain.

Type of pain	Time	Pain Intensity*		p value
		Control	Bupivacaine	
Constant pain	4 hrs	55±12	16±6	p<0.02
	5 days	43±11	4±2	p<0.01
	10 days	7±4	0	NS
Pain on swallowing	4 hrs	77±11	32±11	p<0.02
	5 days	63±10	4±2	p<0.002
	10 days	14±5	0	p<0.05

* scores on a 100 mm visual analog scale (mean ±SEM)

S130

Title: PATIENT MONITORING DURING MRI

Authors: N.A. Jorgensen, M.D., J.M. Messick, M.D., M. Nugent, M.D., J. Gray, Ph.D., T.H. Berquist, M.D., G.S. Forbes, M.D.
Affiliation: Departments of Anesthesiology and Radiology, Mayo Clinic, Rochester, Minnesota 55905

Introduction: Standards for monitoring during general anesthesia have been established by the ASA.(1) Some patients, often because of age or mental status, require a general anesthetic or intravenous sedation for adequate magnetic resonance imaging (MRI). Standard ECG, blood pressure manometers, and capnography systems, though adequate for the 0.15 Tesla scanners,(2) have not functioned well in the 1.5 Tesla scanners. Some pulse oximeters degrade image quality. This study was designed to determine if the monitoring standards could be met with present equipment during 1.5 Tesla MRI scanning without degrading the image.

Methods: With institutional approval and written, informed consent from all volunteers, using identical scanning techniques, MRI images (GE 1.5 Tesla Signa scanner) of the head and chest were obtained in ten volunteers with and without monitoring equipment. The monitoring equipment included a pulse oximeter (different brands), an ECG monitor developed specifically for the MRI environment which transmits signals via a fiberoptic cable, a capnograph, and an automated blood pressure monitor. Temperature was monitored using strips taped to the subject's forehead and read between scanning sequences. Inspired O_2 concentration was monitored using a Clark electrode monitor with modified power source. A portable mass spectrometer and a Raman-scattering based analyzer were used to monitor inspired/expired CO_2 in some volunteers. Radiologists with extensive MRI experience were asked to compare the images with and without the monitoring equipment functioning.

Results: The ECG was readable, although minor baseline artifacts and alteration of the QRS wave and T wave occurred to varying degrees in different subjects. Other monitors functioned satisfactorily during the scanning periods. One pulse oximeter did not cause serious image degradation. The effects of electronic noise generated by the monitoring equipment was apparent in many cases. Single frequency generators produce "zippers" or artifactual lines across the entire image. Other equipment generates "white noise", random noise spread uniformly across the entire image. The addition of "white noise" may be overlooked if direct comparison is not made with and without the monitoring equipment. Gating based on the ECG improved image quality of the heart, although the noise introduced by monitoring was perceptible in noncardiac portions of the images.

Discussion: ASA monitoring standards can be met during 1.5 Tesla MRI scanning if equipment is selected carefully and tested.

References

1. ASA Newsletter. Vol. 50, No. 12, Dec. 1986
2. Anesthesiology 62:80-83, 1985

S131

TITLE: **POSTDURAL PUNCTURE HEADACHE IS MORE COMMON WITH THE PARAMEDIAN APPROACH**

AUTHOR: N. H. JORGENSEN, LCDR, MC, USN
AFFILIATION: U.S. NAVAL HOSPITAL OKINAWA, JAPAN

Introduction: Postdural puncture headache **(PDPH)** is a complication of procedures in which the dura is perforated[1]. Many factors are thought to contribute to the incidence of **PDPH**[2]. This study examined in a single blinded fashion the relationship between the paramedian **(PM)** or the midline **(ML)** approach and **(PDPH)** in 143 consecutive, young, active patients undergoing spinal anesthesia.

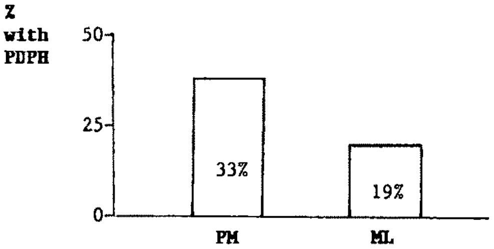
Methods: After obtaining institutional approval and informed consent, each patient was randomly assigned to either a **(PM)** or **(ML)** group. Except for the approach there was no difference in the technique. Only 25g spinal needles were used and were inserted parallel to the fibers. The recovery protocol was the same for all patients. All patients were contacted by phone at least 72° after the dural puncture. **PDPH** was defined as a postural headache appearing with the assumption of the erect position and usually relieved by recumbance[1]. A pain scale of 1-3 was assigned each **PDPH** with "1" defined as a **PDPH** resolving on its own within 24°; "2" defined as a **PDPH** lasting 2-3 days, but resolving on its own; and, "3" defined as a **PDPH** which either because of incapacitating effect or duration greater than 72° required a blood patch. Comparisons were made with the t-test or the critical ratios test as were appropriate to the data.

Results: There was no significant difference in age, weight, sex, duration of attempt or drug used between the two groups. There were 12 **PDPH** (33%) of 31 **PM** spinals and 21 **PDPH** (19%) of 112 **ML** spinals (p less than 0.037), (Fig 1). There was no difference in the distribution within the 1-3 pain scale.

Discussion: **PDPH** is a common phenomenon in our young, active population; however, only 5-7% of them have severe **PDPH** (#3 on the pain scale). This data indicates that the **PM** approach is another factor that contributes to an increased incidence in **PDPH**. Spinal anesthesia can be used in a young population; however, the **PM** approach perhaps should be avoided when possible.

References: 1. Vandam L. D., et al: JAMA 161:586-91, 1956
2. Lybecker H., et al: Anesth Analg 70:389-94, 1990

Fig. 1



S132

TITLE: INTRAVENOUS ATP AMELIORATES CARDIOVASCULAR AND RESPIRATORY FUNCTIONS DURING ANESTHESIA IN SURGICAL PATIENTS

AUTHORS: Y Kaneko,DDS, T Ichinohe,DDS, O Igarashi DDS, T Nakakuki,DDS, AF Fukunaga,MD,PhD
AFFILIATION: Dept. of Anes. Tokyo Dental College, Tokyo, and Dept. of Anes. Harbor/UCLA Medical Center, Torrance, CA 90509

INTRODUCTION: Adenosine and adenosine triphosphate (ATP) have been shown to reduce anesthetic drug requirements. In this study, we examined whether supplemental ATP could inhibit the cardiovascular responses to surgical stress and improve the cardio-pulmonary functions during enflurante(ENF)-nitrous oxide(N_2O)-oxygen(O_2) anesthesia.

METHODS: Following Institutional approval, 14 ASA-1 consenting patients (15-56 yrs) undergoing extensive maxillofacial orthognathic surgery were studied. Anesthesia was induced with IV thiopental (4-5 mg/kg) and intubated with succinylcholine (1 mg/kg). No further muscle relaxants were used. During surgery, anesthesia was initially maintained with 1.34 MAC ENF-N_2O in O_2 with assisted ventilation. Monitoring included EKG (II), radial artery BP, urine output, inspired and expired gases (ENF, N_2O, O_2, CO_2), arterial blood gases, cardiac output (CO), and plasma catecholamines (HPLC). After IV dipyridamole 0.2 mg/kg, ATP was infused continuously into a peripheral vein. Doses of ATP, and ENF or N_2O were then titrated, so that the lowest possible dose of ENF or N_2O were administered in order to establish the new combinations of anesthesia: N_2O-ATP-O_2 (n=7) or ENF-ATP-O_2 (n=7). Normocapnic spontaneous ventilation and normotension were maintained throughout ATP infusion.

RESULTS: Summary of the results are in Table 1. ATP effectively inhibited movent, increase of BP and HR to surgical stimulation, and provided a very stable homeostatic hemodynamic state requiring a maintenance dose of ATP:113±23 μg/kg/min when combined with 60% N_2O alone (n=7) or ATP:103±23 μg/kg/min with 0.9±12% ENF alone (n=7). In both N_2O+ATP and ENF+ATP combinations, there was a significant increase in CO and stroke volume (SV), normal spontaneous ventilation was maintained with improved arterial blood gas data. All patients emerged from anesthesia rapidly and smoothly.

CONCLUSIONS: Our results demonstrate that intravenous ATP, when combined with low doses of inhalation anesthetics may prove to be an effective way to provide anesthesia safely. The potent analgesia of ATP without the cardio-respiratory depression and the rapid action may be very desirable features to be considered in clinical anesthesia.

Table 1

	1.36 MAC ANESTHESIA (n=7)		1.31 MAC ANESTHESIA (n=7)	
	N_2O+ENF	N_2O+ATP	N_2O+ENF	ENF+ATP
N_2O (%)	60%	60%	60%	0
ENF (%)	1.33±0.42	0	1.24±0.48	0.91±0.12
ATP (μg/kg/min)	0	113±19	0	103±23
Hemodynamic:				
HR (bpm)	99±16	95±12	82±11	97±17
SBP (mmHg)	113±21	129±18	114±14	100±19
MBP (mmHg)	79±22	76±16	84±15	61±12*
DBP (mmHg)	63±18	54±15	69±14	44±8*
CO (L/min)	4.3±1.6	6.7±2.4*	5.4±2.5	10.5±1.3*
SV (ml)	44±21	70±23*	65±10	108±23*
Respiratory:				
RR (bpm)	16±4	19±3*	19±3	19±2
pH	7.33±0.04	7.34±0.06	7.37±0.02	7.35±0.02
$PaCO_2$ (mmHg)	45±4	39±3*	47±7	44±7*
PaO_2 (mmHg)	202±28	191±57	215±23	568±50*
BE	-2.0±2.0	-2.4±1.2	-0.4±0.9	-0.5±0.9
Plasma Catecholamines:				
NE (pg/ml)	296±166	429±270	178±102	351±98
EPI (pg/ml)	92±90	153±76	86±19	150±130

mean ± SD * p<0.05

S133

TITLE: MIDAZOLAM LEVELS IN THE ISOLATED CARDIOPULMONARY BYPASS CIRCUIT

AUTHORS: J Keaveny MD, C Clarke MD, B Pleuvry PhD Pharm, DK Whittaker MD

AFFILIATION: Department of Anesthesia, Manchester Royal Infirmary, Manchester, England

Midazolam, a water soluble benzodiazepine, is commonly used as an adjuvant to cardiac anesthesia. It has a short duration of action, produces antegrade amnesia and is stable to the cardiovascular system.Studies have shown falls in plasma concentration of Midazolam and Lorazepan at the onset of cardiopulmonary bypass (CPB), this being attributed to dilution. Fentanyl[1] and Midazolam[2] have been shown to be sequestered by the membrane oxygenator. The purpose of this study was to investigate midazolam sequestration in 10 CPB circuits.

Standard 1/4" PVC tubing circuits containing a Sci. Med. 3-5 membrane oxygenator and a bubble trap were assembled and primed with 500 mls Compound Sodium Lactate, 1000 mls Gelofusin, 210 mls Mannitol, & 7 mmol $MgSO_4$ and 50 mg Heparin. The pump was circulated at 4.5 L/min. and 37°C. At time zero a sample was taken from both arterial and venous sampling ports and 5 mg Midazolam (1mg/ml) was injected upstream of the sampling ports. Further samples were taken at 1,3,5, 10 and 20 minutes. Samples were stored at -20°C and assayed by gas liquid chromatography.[3] Each sample was analyzed three times.

Midazolam levels (mg/ml) expressed as mean and standard deviation (S.D.) were:

Time	Arterial		Venous	
	Mean	SD	Mean	SD
1 min.	1303	828	750	257
3 min.	737	252	696	242
5 min.	585	224	585	239
10 min.	397	149	432	177
20 min.	329	115	316	127

These results suggest that sequestration accounts in part for the fall in plasma concentration during CPB. One set of results showed unexpectedly high Midazolam levels, explained by contamination of the GLC column. At 10 minutes, the Midazolam level had fallen by 85%, which is consistent with a recent study.[2] These results are further evidence to the possibility of administering subtherapeutic doses of anesthetic agents. However, this is an invitro study and the complex interaction of patients, CPB and therapeutic levels need further investigation.

References
1. Koren G, Crean P, Klein J, Goresky G, Villomater J, MaacLeod SM. Sequestration of fentanyl by the cardiopulmonary bypass. Eur J Clin Pharmacol 1984;27:51-56.
2. Silvasi DL, Rosen DA, Rosen KR. Absorption of Midazolam by the Sci-Med membrane oxygenator. Anesth Analg 1989;68:S261.

S134

TITLE: INTERACTION OF TISSUE-TYPE PLASMINOGEN ACTIVATOR WITH HEPATIC CELLS: A MODEL FOR LIVER TRANSPLANTATION

Authors: SD Kelley, M.D., M Csete Prager, M.D., DM Bissell, M.D.°

Affiliation: Departments of Anesthesia and Medicine°, University of California, San Francisco, CA

Introduction: In 25-30% of patients undergoing orthotopic liver transplantation, excessive bleeding due to primary fibrinolysis follows reperfusion of the grafted liver. This bleeding is associated with prolonged increased tissue-type plasminogen activator (t-PA) levels.[1] We propose that the transplanted liver may inadequately clear t-PA. To evaluate this hypothesis, a model system was developed to study the binding of t-PA by hepatic cells.

Methods: Human hepatic cells from hepatoma cell line Hep G2 were plated in 24-well tissue culture dishes with 10^5-10^6 cells per well. Recombinant t-PA was radioiodinated by the chloramine-T method and purified by exclusion chromatography. Binding studies were conducted by incubating cells with 200 pM concentration of ^{125}I-t-PA in serum free media. Following incubation for 5-120 min, cells were washed and cell-associated radioactivity was determined by gamma-ray counting and normalized to 10^6 cells based upon protein content. To determine if the binding was saturable, 2 hour incubations were performed with 1-10 nM concentrations of ^{125}I-t-PA. Total binding of t-PA was determined by incubation with ^{125}I-t-PA alone; nonspecific binding was measured by incubation with 100-fold molar excess of unlabeled t-PA. Specific binding was determined by subtracting the nonspecific binding from total binding. Triplicate sample analyses were performed at each time point.

Results: Radioiodination produced ^{125}I-t-PA with specific radioactivity >10^4 CPM per pM of t-PA. Following exclusion chromatography, the purity of labeled t-PA was 98.1%. With incubation at 25°C, Hep G2 cells showed specific binding of t-PA that reached 33.8 fmol/10^6 cells at 2 hours. At 4°C, specific binding reached 19.1 fmol/10^6 cells. Saturation of binding was apparent at ligand concentrations over 8 nM ^{125}I-t-PA.

Discussion: Human hepatic cells demonstrate specific binding of t-PA that is temperature dependent and saturable. This type of binding interaction is consistent with the prolonged elevated levels of t-PA seen in liver transplant patients. Preservation of the liver graft in ice cold solution may impair the cellular mechanism responsible for plasma clearance of t-PA. Similarly, the development of a high plasma level of t-PA during the anhepatic period[2] may saturate the binding process. This model system will be useful to further elucidate the cellular mechanisms responsible for plasma clearance of t-PA in the transplanted liver and the impact of graft preservation on this process.

References:
[1] Transplantation 47:978-984,1989.
[2] Blood 71:1090-1095,1988.

S135

TITLE: ARTERIAL TONOMETRY FOR BLOOD PRESSURE MONITORING IN PEDIATRIC ANESTHESIA

AUTHORS: O.Kemmotsu,M.D., H.Otsuka,M.D., M.Ueda,M.D., T.Yamamura,M.D., J.S.Ekerle, S.M., D.C.Winter,PhD
AFFILIATION: Dept. Anesth., Hokkaido Univ. Sch. of Med., Sapporo 060, Japan

A newly developed system of arterial tonometry enabled us to continuously and non-invasively monitor the entire blood pressure waveform in addition to determing the systolic and diastolic pressures in patients ranging in age from 8 to 82(1). If we can obtain satisfactory results using this system in small children, the reliability of the method in a challenging situation will have been demonstrated.

Twenty pediatric patients (mean age:3.7 y.o., mean body weight;16.0 kg) were studied after institutional approval and informed consent. Intraarterial blood pressure (IBP) was measured in the either right or left radial artery by a disposable transducer, while tonometric blood pressure (TBP) was made at the radial artery of the other arm.

The shape of the TBP waveform was nearly identical to that of IBP (Fig.). Although systolic precision did not differ among six pressure groups, diastolic precision was best at lower pressures and the worst precision value was obtained for the group over 70 mm Hg (Table).

Our results indicate that the system can provide reliable value of systolic blood pressure in small children. However, TBP performance deteriorates in higher diastolic pressure values with predictable underestimation of diastolic pressure. Further improvements in transducer technology should be needed to achieve satisfactory results.

Reference
1. Anesthesiology 1989;71:A406

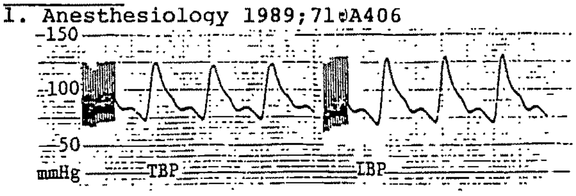


Fig. Simultaneous tracings of TBP (left) and IBP (right) obtained from 3 y.o. male.

Table. Precision (P) and Bias (B)

Systolic	P	B	Diastolic	P	B
all	4.75	1.12	all	5.65	0.24
-79	7.11	6.70	-39	5.67	4.64
80-89	4.19	2.40	40-49	6.47	-5.57
90-99	5.07	1.08	50-59	9.59	-8.12
100-109	4.43	0.06	60-69	9.96*	-8.69
110-119	5.45	0.25	70-	18.25*	-18.25
120-	5.88	-6.21			

*significant vs the lowest pressure range.

S136

Title: DO INTRAOPERATIVE CV COMPLICATIONS PROLONG HOSPITAL STAY FOR SAME-DAY-SURGERY PEDIATRIC PATIENTS?

Authors: P Kerkar, MD and MR Jewell, MD

Affiliation: Children's Hospital of Michigan, Detroit, Michigan

Introduction: The cost advantages of SDS procedures depend greatly on briefness of hospital stay.[1] For pediatric patients there is additional psychic benefit in their early escape from the increased stress and morbidity of hospitalization. Halothane has become the first choice for smooth inhalation inductions; but we prefer methohexitone IM for the 1-4 year olds to eliminate their anxiety and panic of separation from parents. Vecuronium is generally used for intubation and relaxation.[2] Our aim is to evaluate the occurrence and type of intraoperative cardiovascular (CV) complications and their effect on duration of hospital stay.

Methods: Ninety-three patients of ASA status I weighing between 4 and 25 kg. were divided into four groups. (Table 1) Group I and II were induced with halothane and methohexitone respectively, and maintained with halothane and N_2O. Group III and IV were induced with halothane and methohexitone respectively, and maintained with halothane, N_2O and vecuronium. The pulse oximeter, ECG, blood pressure, E.T.CO_2 and % of gases and volatile agents were continuously monitored. D_5LR was started IV after induction and run at 5ml/kg/hr.

Results: The CV complications observed were bradycardia, tachycardia and other dysrrhythmias. The bradycardia yielded hypotension (65 torr systolic) and was treated with IV atropine (0.01 mg/kg). Tachycardias were successfully treated with fentanyl (0.001-0.002 mg/kg). Other dysrrhythmias were treated with lidocaine (1.5 mg/kg). The distribution of complications in different anesthetic groups is tabulated in Table 2. All these patients were sent home within four hours postoperatively. Chi-square test (d.f. 3, p<0.04) did not demonstrate differences of significance in occurrence of CV complications among these four groups.

Discussion: Anesthesia for SDS patients with the described agents yielded a very small occurrence of CV complications. This seems entirely compatible with the priorities of SDS programs. However, our intention is to do a similar review on a much larger population.

Table 1 - Demographic data

Anesthes.	4-10 Kgm.	11-15 Kgm.	16-20 Kgm.	21-25 Kgm.
Group I	6	2	4	5
Group II	8	4	7	9
Group III	12	0	3	8
Group IV	3	16	6	0
Total	29	22	20	22

Table 2 - Complication data

Anesthesia	Gp.I %	Gp.II %	Gp.III %	GP.IV %	Total %
Dysarhythmia	3.23	1.08	0	0	4.30
Tachycardia	0	2.15	0	3.23	5.38
Bradycardia	0	1.08	0	0	1.08
Total	3.23	4.30	0	3.23	10.75

References:
1. Hospitals, G1(12):PB88, 1987.
2. Anesthesiology, 71:840-844, 1989.

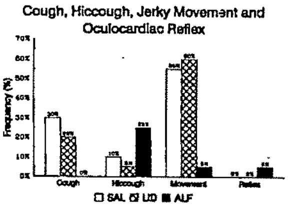
S137

TITLE: ALFENTANIL DECREASES THE JERKY MOVEMENTS AND COUGH ASSOCIATED WITH INTRAVENOUS METHOHEXITAL

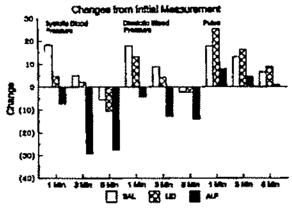
AUTHORS: S.Khalil,M.D., G.Howard,M.S., A.Messamore,M.D., C.Hanis,PhD, R.Ruiz,M.D.
AFFILIATION: Anes. & Opthal. Departments, University of Texas, Houston, TX.

The majority of patients scheduled for cataract extraction are old. The operation is mostly done under retrobulbar block. Administration of a brief general anesthesia for placing the blocks is less stressful to the patients and the associated primary position of the eye decreases the chances of developing ocular complications. A sleeping dose of I.V. Methohexital (M) is commonly used to provide the brief general anesthesia. Patients usually regain their consciousness with a clear sensorium in a short time. But, I.V. M anesthesia may be associated with jerky abnormal movements, cough, hiccough and it may not attenuate the cardiovascular responses associated with placing the retrobulbar blocks. The addition of Alfentanil (A) or Lidocaine (L) to I.V. M may decrease the possible side effects of M anesthesia. In the study, we evaluated the effects of adding A or L to I.V. M on the possible side effects of M anesthesia.

Institutional approval and patient's informed consents were obtained. 60 adult patients, age 50-75 yrs, Class I and II ASA physical status classification were included. The study was double blinded and the patients were randomly assigned to one of three groups, twenty each. The patients in the first gr. received a bolus of A 5 ug/kg I.V., in the second gr. L 1 mg/kg, and in the third gr. Placebo (P), immediately followed by I.V. M 1.5 mg/kg, injected over 30 seconds. In the holding area, after applying the standard monitors, the brief general anesthesia was administered. The retrobulbar block was then placed. The incidence of jerky abnormal movements, cough, hiccough and oculocardiac reflex were recorded. Heart rate, systolic and diastolic B.p while the patient is awake, at loss of lid reflex and at one, three and five minutes from placing the block were recorded. Analysis of variance was used to analyze the data. The groups were similar in age, sex and weight. The incidence of jerky movements and cough were significantly less in the A gr. compared to the P & L grs. The incidence of hiccough and oculocardiac reflex was not different between the groups. A statistically significant rise in heart rate, systolic and diastolic B.p at one and three minutes from placing the block occurred in P and L grs. compared to A gr.



Cough, Hiccough, Jerky Movement and Oculocardiac Reflex



Changes from Initial Measurement

In conclusion we recommend the addition of 5 ug/kg of A to I.V. M anesthesia for retrobulbar blocks, as it significantly depresses the associated jerky movements and cough and significantly attenuates the hemodynamic changes associated with placing the blocks.

S138

TITLE: EVALUATION OF VECURONIUM FOR TRACHEAL INTUBATION IN PAEDIATRIC CARDIAC PATIENTS.

Authors: U Kiran, MD, VR Khyriem, MB, N Saxena,MD

Affiliation: All India Institute of Medical Sceinces, New Delhi (INDIA).

Introduction: Cardiovascular stability is the most essential feature of a muscle relaxant used for tracheal intubation in children with cardiac disease. Suxamethonium though most commonly used but is associated with arrhythmias(1) and potassium disturbances. Pancuronium is reported to produce tachycardia and hypertension(2). Cardiovascular stability is claimed with vecuronium(3). We evaluated vecuronium (0.1 mg/kg) for intubation, haemodynamic response and serum potassium changes which were compared with suxamethonium (2mg/kg) and pancuronium (0.1 mg/kg).

Methods: Sixty cyanotic and actyanotic children in the age range of 1-12 years undergoing cardiac surgery were studied in three groups of twenty each according to the muscle relaxant used. Children were premedicated with morphine 0.3 mg/kg and atropine 0.01 mg/kg im one hour before surgery. They were induced with oxygen and halothane. Parameters studied were a) Onset of muscle relaxation (microtein N.M. stimulator) b) Blood pressure c) pulse rate d) serum potassium at 30 sec., 1,2,4 & 5 min. after the muscle relaxant. Institutional approval and informed consent was obtained for this study.

Results: All the children could be intubated within 3 min. in vecuronium group. Vecuronium provided good intubating conditions in 95% of children alongwith haemodynamic stability. In suxmethonium group, the major problem was of arrythmias (54%) as compared to 4% with both vecuronium and pancuronium. Significant tachycardia was seen with pancuronium. Serum potassium significantly rose with suxamethonium.

Discussion: The haemodynamic stability and good relaxation seen during tracheal intubation in children with compromised cardiovascular system confirms the suitability of vecuronium for sick cardiac patients of paediatric age group.

References:

1. Anesthesiology 42; 41: 1975.
2. Paediatrics 75; 254: 1985.
3. Act. Anaesth. Scand. 24; 393: 1980.

S139

TITLE: INTERPLEURAL BLOCKADE PRODUCES EFFECTIVE ANALGESIA IN THE ELDERLY

AUTHORS: S.J. Kleiman, M.D., S. Wiesel, M.D., A.P. Kliffer, M.D.
AFFILIATION: Departments of Anaesthesia, SMBD-Jewish General Hospital and McGill University, Montreal, Quebec, Canada.

INTRODUCTION: Interpleural blockade is an effective means of delivering postoperative analgesia in patients undergoing cholecystectomy. The elderly may have a reduced postoperative requirement for narcotics[1]. We studied the efficacy of interpleural bupivacaine in a population of elderly patients using a double blind, placebo controlled study.
METHODS: After institutional approval and informed consent, 18 patients over the age of 65 years scheduled for simple cholecystectomy using a subcostal approach were randomly assigned to receive either bupivacaine (BUP, n=8) or saline (CON, n=8). Patients were not premedicated and a standard, non-narcotic anaesthetic was given. After completion of surgery, an interpleural catheter was introduced and the patient was given either 20 ml of bupivacaine 0.5% with epinephrine 1:200,000 (BUP) or saline (CON). Pain scores were elicited every hour using a four point scale. The requirement for supplemental analgesia was noted. All values are presented as mean +/- SEM and groups were compared using the student's t test for independent samples, with $p < 0.05$ considered statistically significant.
RESULTS: Pain scores were significantly lower in the BUP patients at all time points up to 6 hours (Fig. 1). The cumulative requirement for supplemental morphine was significantly less by 8 hours (Fig. 2).
DISCUSSION: Interpleural blockade with 20 ml bupivacaine 0.5% with epinephrine is an effective method of analgesia in the elderly after subcostal cholecystectomy. This conclusion is based on lower pain scores and a reduced requirement for supplemental narcotics.

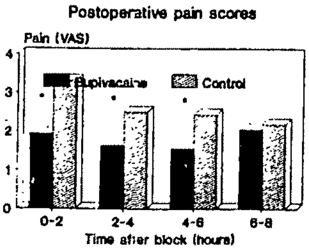


Fig. 1

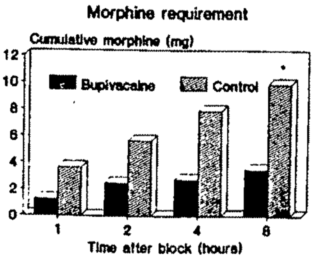


Fig. 2

(1) Anesth Analg 1990; 70: 316-20.

S140

TITLE: INTERPLEURAL BUPIVACAINE DOES NOT LEAD TO ELEVATED PLASMA LEVELS IN THE ELDERLY

AUTHORS: A.P. Kliffer, M.D., S. Wiesel, M.D., W. Lubenskyi, B.Sc., S.J. Kleiman, M.D.
AFFILIATION: Departments of Anaesthesia, SMBD-Jewish General Hospital and McGill University, Montreal, Quebec, Canada

INTRODUCTION: Interpleural blockade is an effective method of delivering postoperative analgesia after cholecystectomy[1]. This study compares the plasma levels attained in elderly patients with non-elderly patients.
METHODS: Institutional approval and informed consent were obtained from a group of elderly patients (age$>$65 years, n=8) and nonelderly patients (age$<$ 65 years, n=8) who were scheduled for simple cholecystectomy using subcostal incision. After termination of the surgery, an interpleural block was performed in the lateral position and initiated with a single dose of 20 ml bupivacaine 0.5% with epinephrine 1:200,000. Blood was collected immediately before the block and up to 300 minutes after. Samples of chloroform extracted plasma were run on HPLC using UV detection with etidocaine as internal standard. Plasma levels were described as mean +/- SEM and comparisons made at all time points. The student's t test was used for independent groups with $p < 0.05$ considered statistically significant. Linear regression analysis was performed in order to relate the peak plasma levels to patient age.
RESULTS: The elderly patients were 72.8 +/- 7.8 years of age (mean +/- SD) compared with 35.5 +/- 14 years in the nonelderly group. Mean plasma levels were higher in the nonelderly group of patients than in the elderly group at all time points before 300 minutes (Fig. 1) but did not reach statistical significance. Peak bupivacaine levels of individual patients were negatively correlated with patient age with a correlation coefficient of 0.22 (Fig.2).
DISCUSSION: The interpleural injection of bupivacaine 20 ml with epinephrine 1:200,000 appears to be safe in the elderly, with peak levels below the toxic range.

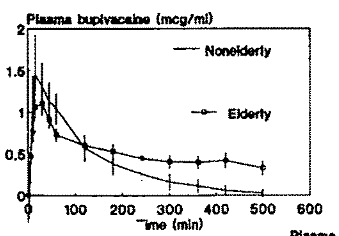


Fig. 1

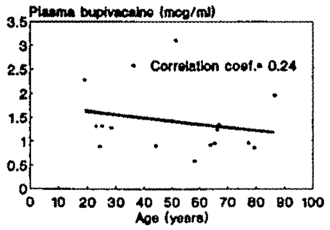


Fig. 2

(1) Anesth Analg 1988; 67: 430-4.

S141

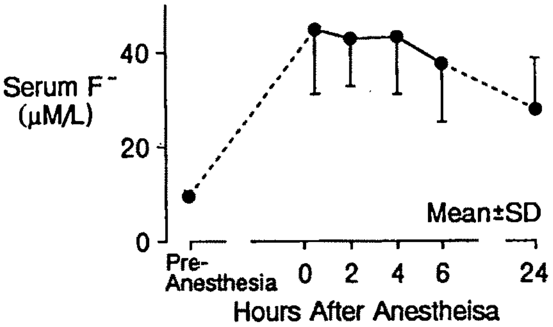
Title: SERUM INORGANIC FLUORIDE CONCENTRATION FOLLOWING ANESTHESIA WITH SEVOFLURANE IN ANURIC PATIENTS

Authors: T Kondo MD, N Yasuda MD, Y Tanifuji MD, K Kobayashi MD, K Miyano MS
Affiliation: Dept of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan

Introduction: The new inhaled anesthetic sevoflurane is metabolized resulting in an increase in serum inorganic fluoride (F^-) concentration in healthy subjects (1). In this study, the extent of increase in serum F^- concentration was investigated in anuric patients.
Methods: With institutional approval and informed consent, 5 chronically anuric patients [age, 45±10 yr (mean±SD)] on dialysis and scheduled for parathyroidectomy were anesthetized with 0.8-1.3 MAC sevoflurane in 50% N_2O. Serum F^- was measured before anesthesia and 0.5, 2, 4, 6 and 24 hr after the administration of sevoflurane was discontinued.
Results: The total dose of sevoflurane was 3.3±0.4 MAC-hours. Maximum F^- concentration was 46±7 μM/L at 0.5 hr and started to decrease at 6 hr after discontinuation of the administration of sevoflurane (Figure).

Discussion: Serum F^- concentration approached 50 μM/L; a concentration which renal failure may occur in patients anesthetized with methoxyflurane (2). However, increase in serum F^- concentration was not prolonged in patients anesthetized with sevoflurane as in patients anesthetized with methoxyflurane. The results suggest that sevoflurane should be administered with caution in patients who have decreased renal function.

References:
1. Holaday DA, et al.. Anesthesiology 1981;54:100-6.
2. Cousins MJ, et al.. JAMA 1973;225:1611-6.



S142

TITLE: PLATELETS IN SHED MEDIASTINAL BLOOD USED FOR POSTOPERATIVE AUTOTRANSFUSION.

AUTHORS: U.E.Kongsgaard, M.D., O.Geiran, M.D., F.Brosstad, M.D., T.Hovig, M.D.
AFFILIATION: Dept. of Anaesthesiology, Surgery, Medicine, and Pathology, Rikshospitalet, 0027 Oslo 1, Norway

INTRODUCTION
Autotransfusion of shed mediastinal blood after open heart surgery has been reported to be a safe procedure (1,2,3,4). The autotransfused blood has undergone coagulation and fibrinolysis, and a relatively high platelet count has been reported (1,2,4). An important question is, however, ---do the platelets present in the reinfused blood function normally?

METHODS
10 patients undergoing open heart surgery received postoperative autotransfusion of shed mediastinal blood collected in the cardiotomy reservoir. Numbers, function and morphology of the platelets found in the autotransfused blood were investigated. Platelets were counted using a Coulter Counter compared with light phase microscopy. Platelet aggregation was measured in a Plyton aggrometer. Dense granule secretion was measured as the extracellular appearance of ADP + ATP with a luceferin-luciferase method. Morphology of platelets was studied with transmission electron microscopy.

RESULTS
Enumeration of platelets using the two methods gave different results. The Coulter Counter gave a mean platelet count of 62,000/ 1, light phase microscopy revealed only a mean platelet count of 10,000/ 1. The platelets failed to aggregate in response to the presence of collagen, and secretion of ADP + ATP was absent. Transmission electron microsopy revealed few platelets, however, a lot of cytoplasmatic fragments smaller or up to the same size as platelets. The platelets found were mostly shape-changed spheroid, characterized with centralization and loss of alpha-granules and dense bodies, changes indicating irreversible platelet activation.

DISCUSSION
Previous studies have shown that shed mediastinal blood have undergone extensive alterations. Thus, it is not surprising to find cell fragments from red blood and other cells that are interpreted as platelets by the Coulter Counter. The function of the few real remaining platelets are furthermore markedly reduced. This fact is important to be aware of when evaluating efficacy and quality of autotransfusion of shed mediastinal blood after open heart surgery. Infusion of larger volumes of autotransfused blood should be supported with platelet concentrates.

REFERENCES
1) J Thorac Surg 75:632-641, 1978
2) Ann Thorac Surg 27:500-507, 1979.
3) Ann Thorac Surg 40:519-520, 1985.
4) J Thorac Cardiovasc Surg 96:178-182, 1988.

S143

TITLE: HAEMODYNAMIC EFFECTS OF HEPARIN DURING CORONARY BYPASS SURGERY.

AUTHORS: U.E.Kongsgaard, M.D.,
N.Smith-Erichsen, M.D.
AFFILIATION: Dept. of Anaesthesiolog,
Rikshospitalet, 0027 Oslo 1, Norway.

INTRODUCTION: Heparin has been suggested as an activator of the the plasma kallikrein-kinin system, with formation of bradykinin, a potent vasodilator (1,2). We wanted to evaluate haemodynamic variables and activation of this protease system after heparin injection.

METHODS: The study received institutional approval. 10 patients with ejection fraction > 40 % undergoing coronary bypass surgery, received heparin (4 mg/kg) and saline (same volume) in a bolus injection at 8 minutes interval, with treatment sequence determined at random, in a double blind, crossover study. Prior to injection of heparin/saline, all surgical stimulation was halted. Anaesthesia was maintained with fentanyl, nitrous oxide and isoflurane. Heart rate (HR), mean arterial (MAP) and central venous (CVP) pressure were recorded. Cardiac output (CO) was recorded continuously with an electromagnetic flow probe placed at aorta ascendence. Systemic vascular resistance (SVR) was calculated at 1 minute intervals. Blood was drawn from the arterial line before and 5 minutes after injection of heparin/saline and analyzed for prekallikrein (PKK), kallikrein-like activity (KK) and functional kallikrein inhibition capacity (KKI), using chromogenic peptide substrate assays. Wilcoxon sum rank test was used to test statistical significans.

RESULTS: MAP decreased in both groups throughout the experimentel period, but significantly more at 2 and 3 minutes after heparin-injection compared with saline-injection. None of the other haemodynamic variables measured were significantly different when comparing heparin- to saline-injection, but there was a tendency to lowering CO and SVR in the heparin group. Heparin-injection resulted in significant changes in the kallikrein-kinin system; increased KK, with reduction in PKK and KKI. No changes in the protease system were recorded after saline-injection.

DISCUSSION: We found a moderate decrease in MAP whether the patient received saline or heparin, possibly because of anaesthetic circulatory depressant action during the abscence of surgical manipulation. If the significant larger decrease in MAP 2 and 3 minutes after heparin-injection was caused by activation of the plasma kallikrein-kinin system, we would expect a decrease in SVR as well, caused by bradykinin, liberated from high molecular weight kininogen. However, no significant differences in SVR or CO took place whether the patiens received saline or heparin. Thus, the plasma kallikrein-kinin system, though apparantly activated after heparin-injection, does not contribute significantly to the decrease in MAP. Therefore, other mechanisms causing decrease in arterial blood pressure, such as acute lowering of ionized calcium, may be involved (3,4).

REFERENCES

1) Acta Anaesthesiol Scand 1989;33:342-347.
2) J Lab Clin Med 1970;76:790-798.
3) J Thorac Cardiovasc Surg 1986;91:303-306.
4) Anesth Analg 1990;70:S204.

S144

TITLE: EFFECT OF ESMOLOL ON HEMODYNAMICS AND INTRAOCULAR PRESSURE RESPONSE TO SUCCINYLCHOLINE AND INTUBATION

AUTHORS: A Kovac MD,P Bennetts CRNA,S Ohara MD,
B LaGreca MD, J Khan MD, J Calkins MD
AFFILIATION: Depts. of Anesth., Ophthal. and OB/GYN,
U. of Kansas Med. Ctr., Kansas City, KS

Administration of succinylcholine (SCC) followed by endotracheal intubation (ETI) causes a rise in intraocular pressure (IOP). Numerous pretreatment methods such as alfentanyl (ALF) have attenuated the rise in IOP related to the administration of SCC followed by ETI (1). The effect of esmolol (ESM) on hemodynamics and IOP in combination with ALF has not been previously reported. The purpose of this study was to determine the effect of ESM on the hemodynamics and IOP response to SCC and ETI following low dose ALF premedication.

This study was approved by the Human Subjects Committee and informed consent obtained from each patient. Study patients (n=20) were ASA Class I-II female patients scheduled for outpatient laparoscopy under general endotracheal anesthesia. Heart rate (HR) was monitored by EKG, mean arterial pressure (MAP) by automated cuff, and IOP by Oculab Tonopen® tonometer (Oculab Inc., Glendale, CA). All patients received ALF 10 mcg/kg as a preop 4 min prior to induction of anesthesia. Study patients (n=10 in each group) received either ESM 1.5 mg/kg or placebo (normal saline) 30 sec prior to induction (150 sec after ALF and 90 sec prior to ETI) in a randomized, double-blind, prospective design. Anesthesia was induced with pentothal 5 mg/kg and SCC 1 mg/kg. Post intubation, N20 70%/02 30% and forane 1% was administered. Measurements (HR, MAP, IOP) were made at baseline, and at 1,2,3,4,5, and 6 min post study drug (time zero). Analysis of variance was used to analyze data. A $p<0.05$ level was set for statistical significance.

The mean age (±SD) was 33 ± 9 years and mean weight was 62±13kg. ESM 1.5 mg/kg blunted the maximum increase in HR (Fig 1), but not MAP or IOP (Fig 2).

Another study showed ALF decreased MAP but not HR at a dose of 15 mcg/kg (2). Our data indicates ESM 1.5 mg/kg, when given 150 sec after ALF 10 mcg/kg (30 sec prior to induction and 90 sec prior to ETI) is effective in attenuating HR, but not the IOP or MAP response to SCC and ETI. In an eye patient with coronary artery disease to whom tachycardia may be detremental, ESM may be a useful adjunct to low dose ALF in attenuating the HR response to laryngoscopy and ETI.

1. BR J Anaesth 1989; 63:688-691
2. Anaesthesia 1984; 39:883-887

Figure 1:
HEART RATE (mean +/- SEM)
(N = 10)

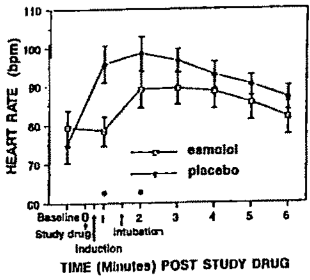
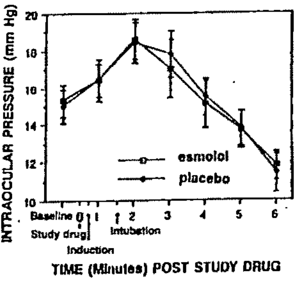


Figure 2:
INTRAOCULAR PRESSURE (mean +/- SEM)
(N = 10)



*Significant difference between esmolol and placebo ($p < 0.05$)

S145

TITLE: IV RANITIDINE REDUCES NAUSEA AND VOMITING AFTER PROPOFOL-ISOFLURANE ANESTHESIA

AUTHORS: B.J. Kraynack, M.D.; M.F. Bates, CRNA

AFFILIATION: Day Surgery Center, Community General Hospital, Reading, Pennsylvania

Introduction:

Postoperative nausea and vomiting (N+V) remain the most common anesthesia-related side effect in outpatient surgery. Ranitidine (RAN), 150 or 300mg, orally the night before surgery and 2-3 hours prior to surgery followed by gastric suctioning (GS) at the termination of surgery significantly reduces the incidence of N+V in female outpatients undergoing laparoscopy with thiopental-isoflurane anesthesia.[1,2,3] Because not all outpatients can be treated the night before surgery, it was of interest to determine if RAN given 2-3 hours prior to surgery could decrease the incidence of N+V in female outpatients undergoing laparoscopy under propofol-isoflurane.

Method:

Institutional approval and informed consent was obtained. Forty adult female patients undergoing outpatient diagnostic laparoscopy were tested. These patients received RAN 50mg in 100cc NSS intravenously (IV) over 20-30 minutes, 2-3 hours prior to anesthesia induction. GS was performed at the termination of surgery. The anesthesia and recovery regimens were previously reported.[1,2,3]

Results:

IV RAN decreased the incidence of N+V to 5%. These results are not significantly different (Chi square) to those we previously reported,[2] in which RAN 300mg orally the night before surgery and 2-3 hours before surgery reduced the incidence of N+V to 4%. In comparison, untreated controls (N=50) suffered a 42% incidence of N+V. The mean time to discharge of IV RAN treated patients was 69.4 ± 3.5 minutes (range 45-135) [not significant (ANOVA) from untreated control time to discharge of 76.4 ± 8 minutes].

Discussion:

This study demonstrates the antiemetic effect of GS and RAN 50mg given 2-3 hours prior to surgery. The reduction in the incidence of N+V (5%) is similar to that previously reported[1,2,3] for oral RAN 150 or 300mg treatment regimens (4%). Significantly, the time to a "street fit" condition following propofol induction is shorter by almost 60%.[1,2,3] Moreover, untreated controls have prolonged times to discharge because of N+V. The few RAN treated patients that remained for prolonged periods postoperatively did so because of pain.

We conclude that IV RAN and GS decrease the incidence of N+V. This regimen is as effective as oral RAN and GS regimens. Finally, when compared to thiopental, propofol combined with RAN, GS, and isoflurane may be the outpatient anesthetic regimen of choice due to a very short recovery time.

References:

[1] Anesthesia Analgesia 70(2S): S218, 1990.
[2] Anesthesiology 1990 (in press).
[3] Anesthesiology 1990 (in press).

S146

Title: **IS ANERGY SOON AFTER MULTIPLE TRAUMA REALLY ASSOCIATED WITH A POOR OUTCOME?**

Authors: HG Kress, M.D., A Woltmann, M.D.
Affiliation: Dept. of Anesthesiology, University of Würzburg, D-8700 Würzburg, FRG

Infection is a frequent cause of morbidity and mortality after multiple trauma. Although impaired immune function has been assumed to be associated with the development of infection in trauma victims, its predictive role is still controversial. In the present prospective study, the predictive value of the cutaneous delayed type hypersensitivity (DTH) response to 7 recall antigens was compared with serial determinations of routine clinical parameters.

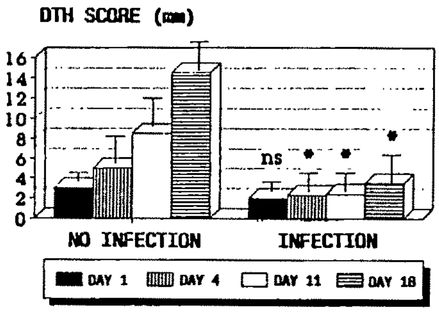
Methods: The study was approved by the institutional ethics committee. 35 consecutive multiple-trauma patients (4 females, 31 males), who had been admitted to the intensive care unit (ICU) because they required controlled ventilation, were prospectively followed during their treatment in the ICU. The extent of trauma was assessed by the Injury Severity Score (ISS). The occurrence of infections and/or death was documented by only one investigator. FIO_2, lactate, creatinine, platelet count, white blood cell with differential count were determined every day. Using the commercially available Multitest[R] device (1), the DTH response to 7 standardized recall antigens was tested at defined time intervals.

Results and Discussion: The overall ICU mortality rate was 23%. In survivors, the mean ISS was 29.5, in nonsurvivors 38.9 ($p<0.05$). Mortality significantly increased with sepsis ($p<0.01$). Interestingly, the DTH response and the severity of trauma did not show any interdependence. Immediately after ICU admission (day 1), the DTH response failed to correlate with either infection or the mortality rate: most of the patients were anergic on initial testing (Fig.). In this early stage, the serum levels of creatinine or lactate, the lymphocyte and the promyelocyte counts and the fraction of inspiratory oxygen (FIO_2) proved to be more reliable predictors ($p<0.05$). Beginning on the 4th day after trauma, however, a good correlation was found between the sequential skin test results and the development of infection (Fig.). In conclusion, lactate, FIO_2 and white blood cell counts are early indicators of an impending poor outcome, whereas the DTH response is not. In the later course, however, DTH scores below 5 mm identify multiple-trauma patients at increased infectious risk.

References:

1. Kniker WT, Anderson CT, Roumiantzeff M. *Ann Allergy* 1979; 43:73.

Figure:



S147

Title: RINGER'S ACETATE OR DEXTRAN 70, WITH OR WITHOUT HYPERTONICITY, IN THE TREATMENT OF ENDOTOXIN SHOCK IN PIGS.

Authors: J. Kristensen, M.D. & J. Modig, M.D., Ph.D.
Affiliation: Department of Anesthesiology, University Hospital, Uppsala, Sweden.

Introduction: Controversy exists whether crystalloid or colloid should be used in the treatment of septic or endotoxin shock. Shock treatment with small volumes of hypertonic saline in hemmorrhagic shock improves cardiovascular function. Since this treatment has not been systematically investigated in endotoxin shock, we tested whether administration of hypertonic solutions, alone or combined with dextran 70, could beneficially influence treatment of endotoxin shock.

Methods: 30 pigs weighing 18-32 kg were used. Anesthesia was maintained with a continuous i.v. infusion of chlormethiazole and pancuronium. Throughout the experimental period the animals were ventilated with air. After completed catheterization, baseline measurements were obtained and an i.v. infusion of E. coli endotoxin (18 ug/kgxh; 0111:B4) was started and continued throughout the experimental period of 8h. When shock was achieved the pigs were allocated to 5 treatment groups, each of 6 pigs. Definition of shock: Qt and MAP <50% of baseline, SVO_2 <35% and BE <-7mmol/l. In the Ringer group the pigs were treated with Ringer's acetate throughout the experimental period. In the hypertonic saline (HS) group the animals received 7.5% NaCl, 10 ml/kg infused over 4-7 min. A third group was initially treated as the HS group, followed by 6% dextran 70 for 60 min (HS+D). In the pure dextran group the pigs were treated with 6% dextran 70 for 60 min (D). The mixed hypertonic saline-dextran (HSD) group was treated as the HS group, the NaCl was dissolved in 6% dextran 70, making the solution both hypertonic and hyperoncotic. In all groups treatment was aimed at a stable MLAP. 3-factor (crystalloid-colloid, isotonic-hypertonic, time) analysis of variance was used. The study was approved by the local animal Ethics Committee.

Results: After 3 h shock was achieved and treatment was started. Hypertonicity (HS, HS+D and HSD) did not show any advantages over isotonicity (Ringer's acetate and D). Only transient beneficial effects on Qt, MAP, SVO_2 and O_2-del. lasting for less than 30 min, were seen. The colloid factor (all solutions containing dextran; D, HS+D and HSD) did show advantages over the crystalloid factor (Ringer's acetate and HS) regarding both Qt, MAP, SVO_2, O_2-del. and survival. Administration of Ringer's acetate resulted in a deterioration of pulmonary function. It was difficult to elevate MLAP or even to keep it at baseline level and Qt was only transiently increased although more than 10 times the dextran volume was given in the Ringer's acetate regimen. The results in the HS and Ringer groups were a deterioration of O_2-del. and a poor survival.

Conclusion: Dextran 70 is superior to Ringer's acetate in resuscitation from endotoxin shock in pigs. We found no role for the use of hypertonic NaCl, alone or in combination with dextran, in the treatment of this type of prolonged endotoxin shock.

S148

TITLE: UNEXPECTED RISK FACTORS FOR THE DEVELOPMENT OF HYPOTENSION DURING ANESTHESIA

AUTHORS: R KROSS MD, N SHAH MD, S SHAH MD, R ALAGESAN MD, R RODMAN MD
AFFILIATION: MEMORIAL SLOAN-KETTERING AND CORNELL UNIV, NY,NY 10021

INTRODUCTION: Intraoperative hypotension is associated with myocardial ischemia and infarction.[1] While hypertensive individuals are recognized to be at risk for hypotension,[2] other preoperative risk factors that might serve as a warning signal are as yet undetermined. We therefore searched our computerized Quality Assurance database in an attempt to identify heretofore unidentified risk factors for the development of intraoperative hypotension in general surgical patients.

METHODS: The records of all anesthetics administered over a 2-month period were studied. The incidence of hypotension, defined as low BP requiring vasopressor therapy, was tabulated. Suspected risk factors included: operation, history of hypertension, prior cardiovascular (CV), pulmonary, renal or endocrine disease, and previous radiation therapy or chemotherapy.

RESULTS: Among 2,711 anesthetics, hypotension occurred in 121. Of these, 36 had no recognizable risk factor, whereas 85 had one or more risk factors ($P<.005$ by Chi-square analysis). As expected, CV disease was the most likely risk factor (a 42% incidence among all hypotensive patients). When patients with concurrent CV disease were removed from further consideration (table), we were surprised to note that the next highest risk factors for intraoperative hypotension were previous chemotherapy or radiation.

Risk Factor	Total Hypotensive	Hypotensive Pts No CV disease:
	No.	No. (%)
Renal Disease	4	1 (3)
Diabetes	11	4 (12)
COPD	12	6 (18)
Radiation	27	11 (32)
Chemotherapy	16	12 (35)

DISCUSSION/CONCLUSIONS: Since the incidence of previous radiation or chemotherapy in our surgical population does not approximate the frequency with which these patients became hypotensive under anesthesia, we conclude that these preoperative treatments should be considered as potential risk factors for intraoperative hypotension.

BIBLIOGRAPHY: 1. Goldman L, Caldera DL: Anesthesiology 50:285, 1979. 2. Prys-Roberts C, et al: Br J Anaesth, 1984,56:711.

S149

Title: EPIDURAL OPIOIDS AND LIDOCAINE GIVEN BEFORE BABY DELIVERY FOR CESAREAN SECTION IN CHINESE PARTURIENTS: EFFICACY AND SAFETY

Authors: WF Kwan, M.D., EC Chuah, M.D., BJ Chen, M.D.
SY Wong, M.D.
Affiliations: Chang Gung Memorial Hospital, Taipei,
Taiwan, and Dept. of Anesthesiology
Harbor-UCLA Medical Center, Torrance, CA

Epidural opioid for post-cesarean section (C/S) analgesia has become popular. We studied the efficacy and safety in the mother and baby of adding five different opioids to 2% Lidocaine for C/S before baby delivery in Chinese parturients.

Institutional approval and written informed consent were obtained. Ninety healthy parturients who had epidural anesthesia (2% Lidocaine with 1:200,000 epinephrine) for elective C/S were randomly divided into 6 groups of 15 each, and assigned to receive Saline(S) 3ml, Morphine (M) 3mg, Demerol(D) 25mg, Fentanyl(F) 50ug, Butorphanol(B) 2mg, or Nalbuphine(N) 5mg, [opioids were diluted with Saline to 3ml] through the catheter at the onset of epidural blockade. Intraoperative pain was measured using a rank score (none, mild, moderate or severe) at skin incision, bladder retraction, delivery, uterine repair, and skin closure. Pain free interval (time from injection to when patient experienced any pain), duration of analgesia (time from injection to the first dose of analgesic requested by the patient), maternal side effects and Apgar scores were recorded. The data were analyzed with Chi-square or ANOVA and $p < 0.05$ was considered significant.

The six groups were demographically similar. 18-23 ml of 2% Lidocaine were required to achieve T4 analgesia level. Intraoperative analgesia was improved by adding opioids (except M) before baby delivery. Slow onset of M makes it less effective. Incidence of nausea was higher in patients receiving opioids. Somnolence occurred more frequently in patients given B. However, these side effects were mild and easy to manage. All infants (except 1 baby with D) had Apgar scores above 7 at 1 min and above 8 at 5 min indicating good neonatal outcome. The low 1 min Apgar score (3) in this baby may be due to prolonged uterine incision to delivery interval (4 min). Pain free intervals were similar to other studies. Duration of analgesia was longer in Chinese parturients (1,2,3) which may be attributable to the cultural factor, e.g. Chinese would usually rather suffer pain than take medication.

In conclusion, it is safe and beneficial to add a small dose of opioids including M,D,F,B or N to Lidocaine for C/S before baby delivery. Chinese parturients require less postoperative analgesics.

References: 1. Anesthesiology 63:694-698,1985.
2. Anesth Analg 66:887-893,1987.
3. Anesth Analg 62:667-672,1983.

Lidocaine +	S	M	D	F	B	N
Pruritis N (%)	0(0)	3(20)	2(13)	1(7)	1(7)	0(0)
Nausea N (%)	3(20)	7(47)	8(53)	7(47)	8(53)	8(53)
Vomiting N (%)	0(0)	2(13)	2(13)	1(7)	0(0)	1(7)
Somnolence N (%)	0(0)	2(13)	1(7)	1(7)	4(27)*	1(7)
Respiratory depression N (%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Pain free interval (hrs)	3.3	18*	7.0*	6.4*	7.8*	8.0*
Duration of analgesia (hrs)	12.4	27.8*	14.8	12.7	13.7	13.8

* $P < 0.05$ in comparison to the control group.

S150

Title: EMERGENCE FROM DESFLURANE (I-653) OR ISOFLURANE ANESTHESIA AT 0.65 MAC WITH 60% NITROUS OXIDE

Authors: W-F Kwan, M.D., C. Lee, M.D., S.K. Tsai, M.D., B-J Chen, M.D., E. Cantley, R.N.
Affiliation: Dept. of Anesthesiology, Harbor-UCLA Medical Center, Torrance, CA 90509

Desflurane (DF) is a new volatile anesthetic with a low blood:gas solubility coefficient of 0.42. Our previous study indicated that at 1.25 MAC in O_2, DF is faster than isoflurane (IF) in emergence from anesthesia.[1] The present study concerns DF and IF at 0.65 MAC with 60% nitrous oxide (N_2O) in O_2.

With institutional approval, twenty-five informed and consenting adult patients, ASA I, male, age 18-42 y.o., undergoing elective orthopedic surgery were studied. As premedication, midazolam 1-2 mg was given i.v. in divided doses. We monitored ECG, O_2 saturation, BP, core temperature, end-tidal CO_2 ($ETCO_2$), and concentrations of N_2O, O_2 and inhaled and exhaled DF or IF (Datex^R). Anesthesia was induced with thiopental 5 mg/kg, followed by 2 mg/kg in 2 min, and continued with DF (n=16) or IF (n=9) with N_2O. Patient entry was randomized. The trachea was intubated under deep anesthesia (2 MAC) without the use of any relaxant. The anesthesia was then maintained at DF 4.6% or IF 0.8% exhaled (both 0.65 MAC for this population), with 60% N_2O in O_2. $ETCO_2$ was maintained at 32-35 torr and core temperature at 36-37°C. Fentanyl 50 ug was given 30 min before discontinuing the anesthetics. Toward the end of surgery, normal $ETCO_2$ was restored and neuromuscular block fully reversed. DF or IF and N_2O were turned off simultaneously. The patient's first spontaneous motion, cough, and response to painful pinch and verbal command were recorded. Orientation to age, name and body parts were assessed in a uniform fashion at 1-min intervals until all 3 ("triple orientation") were achieved. Data were presented as mean ± SEM and compared by Student's t-test. The average age was 28 ± 1.8 for DF and 26 ± 2.0 for IF. The duration of anesthesia was 146 ± 17 and 149 ± 23 min, respectively. The table shows faster awakening from DF. There was no significant difference in time to cough, spontaneous movement or reaction to painful pinch.

DF is superior to IF in emergence, both at 1.25 MAC in O_2 and at 0.65 MAC + 60% N_2O in O_2. Comparing DF and N_2O, DF 0.65 MAC + N_2O 60% in O_2 has a shorter emergence time than DF 1.25 MAC in O_2 (10.9 ± 0.9 min vs. 16.9 ± 1.5 min to "triple orientation", respectively, $p < 0.05$). In other words, near-equipotent substitution of 0.65 MAC of DF with 60% N_2O speeds up the recovery. We conclude that in combination with N_2O, DF remains faster in emergence than IF, but that DF is slower than N_2O in spite of a lower blood:gas solubility coefficient (DF=0.42, N_2O=0.46).

Reference:
1. Anesthesiology: 1990 ASA Annual Meeting (in press)

Recovery from DF or IF 0.65 MAC + 60% N20 (min):

	Spontaneous movement	Eye opening	"Triple orientation"
DF + N_2O	5.8 ± 0.8	7.8 ± 0.7*	10.9 ± 0.9*
IF + N_2O	7.9 ± 1.3	14.0 ± 1.9	18.6 ± 2.5

* $p < 0.05$ DF vs. IF

S151

Title: THE COST OF WASTED ANESTHETIC GASES

Authors: S. Lampotang, ME; M.E. Nyland, BA; and N. Gravenstein, MD
Affiliation: Depts. of Anesthesiology, Neurosurgery, and Mechanical Engineering, Univ. of Fla., Gainesville, FL 32610-0254

The anesthetic efficiency, η, of a circle anesthesia circuit can be expressed in terms of the rate of mass inflow of anesthetic into the circuit ($\dot{W}_{FGF}$), and the rate of mass outflow of anesthetic through the adjustable pressure limiting (APL) valve ($\dot{W}_{APL}$), where F_1 is the ratio of mean exhaled to mean inhaled anesthetic volumetric concentrations and F_2 is the ratio of fresh gas flow rate (FGF) to respiratory minute volume (MV)[1]:

$$\eta = \frac{\dot{W}_{FGF} - \dot{W}_{APL}}{\dot{W}_{FGF}} \cdot 100 = \frac{1 - F_1}{1 + F_1F_2 - F_1} \cdot 100.$$

A study on cost containment noted that FGF ranged from 2 to 10 l/min with an 87.5% incidence of 5 L/min,[2] which we will assume to be the mean as well as the mode. Assuming an average MV of 7 L/min, a representative F_2 is 5/7 = 0.714. Based on previously reported data,[3] a combined F_1 for halothane, enflurane, and isoflurane is estimated to be 0.6. Average η for a circle anesthesia circuit is therefore 48%. η is overestimated because the ratio of alveolar to inhaled anesthetic concentrations is used,[3] whereas F_1 uses the mean exhaled anesthetic concentration. For simplicity, this η is assumed to be representative of all anesthesia circuits. For halothane, enflurane, and isoflurane, respectively, the current prices ($) per ml of liquid anesthetic are 0.0462, 0.433, and 0.675; the worldwide annual production (tons) is estimated at 1,000, 220, and 800[4]; and the densities (g/ml liquid anesthetic) are 1.86 (20°C), 1.517 (25°C), and 1.496 (25°C).[5] If US prices are representative, total annual world expenditure on anesthetics is therefore roughly $450 million. Assuming an overall η of 48%, about $233,000,000/ yr of anesthetics is wasted worldwide, not including the cost of N_2O and O_2.

This estimate of anesthetic waste may increase 16-fold if I-653, a new, improved volatile anesthetic reportedly with both a cost and a MAC 4 times higher than those of isoflurane, becomes widely used. Furthermore, the blood solubility of I-653 is reportedly comparable to that of N_2O; this has the effect of increasing F_1 to 0.95[3] and consequently decreasing η. Uniformly decreasing FGF to 2.5 L/min while maintaining the anesthetic concentration in the FGF improves overall η to 65% and would save approximately $225,000,000/yr worldwide.

References

1. Schreiber P: Anaesthesia Equipment Performance, Classification, and Safety. Springer-Verlag, 1972, p 118
2. ANESTHESIOLOGY 51:S354, 1979
3. Eger EI: Isoflurane (Forane). A Compendium and Reference. BOC, 1985, p 16.
4. Lancet 1:1209, 1989
5. Dorsch JA, Dorsch SE: Understanding Anesthesia Equipment, 2nd ed. Williams & Wilkins, 1984, p 79

S152

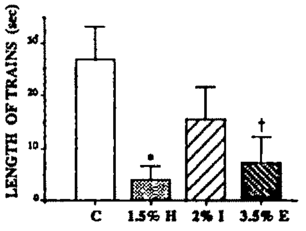
Title: INHALATION ANESTHETICS AND TRIGGERED SUSTAINED RHYTHMIC ACTIVITY IN PURKINJE FIBERS FROM INFARCTED CANINE HEARTS

Authors: A Laszlo MD, JL Atlee MD, S Polic MD PhD, JP Kampine MD PhD, and ZJ Bosnjak PhD
Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

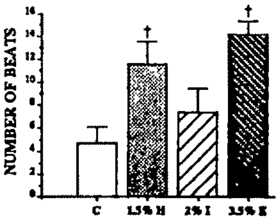
Among the cellular electrophysiologic mechanisms for impulse initiation in Purkinje fibers (PF) surviving 1-4 days following myocardial infarction is triggered sustained rhythmic activity (triggered activity) from delayed afterdepolarizations (DAD).[1,2] Anesthetic effects on such triggered activity have not been described, although one recent report indicates that halothane antagonizes DAD-induced triggered activity due to toxic ouabain in canine PF.[3] The present report compares the effect of equipotent anesthetic concentrations of H, isoflurane (I) and enflurane (E) on triggered activity in PF from 24-hour-old infarcted canine hearts.[4]

After institutional approval, PF from 24-hour-old infarcted canine hearts (N=31)[4] were superfused at 4 ml/min with Krebs solution (37°C) equilibrated with a 97% O_2 - 3% CO_2 gas mixture containing no anesthetic (control = C) or one of the three anesthetics (H, I, or E). The following vaporizer settings were equivalent to measured superfusate concentrations (gas chromatography): 1.5% H = 0.47 mM; 2% I = 0.44 mM; 3.5% E = 0.94 mM. Standard microelectrode techniques were used, and PF were always quiescent under C conditions or with anesthetics. Recorded data include the resting membrane potential under C conditions (80.8±0.7 mV), the number of paced beats (cycle length = 800 msec) required for DAD-induced triggered activity, and length of trains (sec) of triggered activity following cessation of pacing. Data are given as mean±SEM, and paired and unpaired t-tests were used for statistical comparisons.

Anesthetic effects on the number of paced beats for and length of trains of DAD-induced triggered activity are compared to respective C values in the bar graphs below.



* p<0.02 and † p≤0.005 vs. CONTROL (C)



† p≤0.005 vs. CONTROL (C)

Compared to C, H and E, but not I reduce the duration of DAD-induced triggered activity in surviving PF from 24-hour-old infarcts. All anesthetics, but E>I, increased the number of paced beats required to provoke such triggered activity. If observed DAD-induced triggered activity is due to intracellular Ca^{2+} overload, and/or abnormalities in the sequestration and release of Ca^{2+},[5] our results suggest that I among the available potent inhalation anesthetics least interferes with one or more of these mechanisms for triggered activity, and would be expected to show less antiarrhythmic potency against clinical arrhythmias due to triggered activity.

References: 1. *Circulation* 71:813, 1985; 2. *Circulation* 71:1244, 1985; 3. *Anesthesiology* 71:695, 1989; 4. *Circulation* 1:1318, 1950; 5. *Anesthesiology* 72:347, 1990

S153

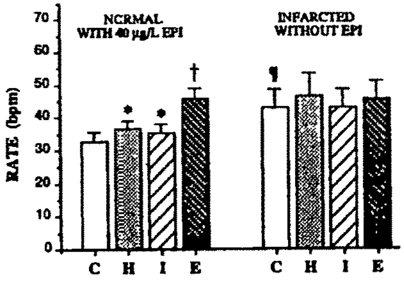
Title: EFFECTS OF INHALATION ANESTHETICS ON NORMAL AND ABNORMAL AUTOMATICITY OF PURKINJE FIBERS

Authors: A Laszlo MD, ZJ Bosnjak PhD, S Polic MD PhD, JP Kampine, MD, PhD, LA Turner MD, and JL Atlee MD
Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

Spontaneous diastolic (phase 4) depolarization normally occurs in cells of the sinus node and subsidiary pacemakers within the atria, AV junctional region, or His-Purkinje system (Purkinje fibers-PF). Such automaticity is considered normal as compared to abnormal automaticity that is sometimes observed in partially depolarized ventricular muscle or PF.[1] Abnormal automaticity may be the mechanism for some ventricular arrhythmias occurring within the first 72 hours of myocardial infarction.[2] While halothane (H) has been reported to slow normal automaticity of PF exposed to epinephrine (EPI),[3] the effects of isoflurane (I) or enflurane (E) on normal automaticity of PF have not been reported. Neither have the effects of H, I, or E on abnormal automaticity been reported. This study examined the effects of H, I and E on normal and abnormal forms of automaticity in canine PF.

After institutional approval, PF from normal (N=24) or 24-hour-old infarcted canine heart (N=34)[4] were superfused at 4 ml/min with Krebs solution (37°C) and equilibrated with a 97% O_2-3% CO_2 gas mixture. EPI (40 µg/L) was used to induce automaticity in PF from normal hearts; PF from infarcted hearts beat spontaneously without EPI. Maximum diastolic potential (MDP) was recorded using standard microelectrode techniques. The following vaporizer settings were equivalent to measured superfusate concentrations: 1.5% H = 0.47 mM; 2% I = 0.44 mM; 3.5% E = 0.94 mM. Control (C) was no anesthetics; data are shown mean±SEM; statistical comparisons were by paired and unpaired t test.

MDP was higher in PF from normal hearts (-85.3±0.8mV) compared to infarcted hearts (-76.6±1.7mV) ($p<0.001$). The effect of H, I, or E on spontaneous rate of PF from normal or infarcted hearts is shown in the figure.



* $p<0.02$ vs. C; † $p<0.001$ vs. C; ¶ $p<0.005$ vs. NORMAL C

H and I produced a similar, small increase in the rate of normal PF exposed to EPI; E produced an even greater increase ($p<0.001$) in this rate . In contrast, the rate of PF derived from infarcted hearts was not affected by anesthetics. These findings might be explained by differing ionic mechanisms for automaticity arising from two levels of MDP[1]. If clinically applicable, our results suggest that H, I or E should not affect or might even increase the rate of ventricular escape rhythms in patients with heart block. Additionally, H, I or E should not affect the rate of idioventricular rhythm in patients with acute myocardial infarction.

References: 1. *Anesthesiology* 72:347,1990;
2. *Circulation* 53:56, 1975; 3. *Anesthesiology* 33:602, 1970.
4. *Circulation* 1:1318, 1950.

S154

Title: AGE AND OUTCOME AFTER CRANIOTOMY

Authors: A.J. Layon, MD; B.E. Burke, RN; and T.J. Gallagher, MD;
Affiliation: Depts. of Anesth., Med., and Surg., Univ. of Fla. College of Medicine, Gainesville, FL 32610-0254

Introduction. Medical care consumes approximately 11% of the gross national product in the United States. As a potential remedy to this purported fiscal crisis, age is being discussed as a criterion to ration health care (1,2). Sometimes (3) but not always (4), this implies elderly patients consume more and benefit less from medical care than younger patients. We studied whether this is true in a group surgical intensive care unit (SICU) patients.

Methods. From a computerized SICU database containing standardized information collected on all SICU patients at the time of admission and throughout SICU stay, we extracted data on each patient who had undergone craniotomy for brain tumor from February 1989 through June 1990. We compared outcome between patients older and younger than 64 yr. Outcome variables included APACHE II scores, number of days in the ICU, and number/type of complications occurring during ICU stay. Data were analyzed by unpaired t, chi-square, Fisher's exact, and covariant analysis tests; $P < 0.05$ was considered significant.

Results (Table). Of 1156 patients admitted to the SICU, 80 (6.9%) met the study criteria. Nine in the younger group and two in the elderly group suffered complications. Except for APACHE II score, which was significantly more severe in the elderly group, study variables did not differ between the two age groups.

Discussion. These data, together with others (4), indicate that, in the population we studied, age over 65 yr is not a determinant in duration of or outcome from ICU stay.

References
1. N Engl J Med 1990; 322:1810
2. N Engl J Med 1990; 322:1813
3. Chest 1989; 96:1120
4. Crit Care Med 1990; 18:694

Table. Difference Between Two Ages of Patients Admitted to a Surgical Intensive Care Unit (SICU)

Demographics and Outcome Variables	Age of Patients (yr) ≤ 64 (n=69)	> 64 (n=11)	P
Age (yr)	41.4 ± 14.9	71 ± 5.8	--
Sex (%)			0.67
Female	58	55	
Male	42	45	
Stay in SICU (days)	1.67 ± 1.53	2 ± 2	0.52
APACHE II score			
On SICU admission	4.1 ± 3.5	9 .8 ± 3.9	0.0001
On SICU discharge	2.6 ± 3.0	7 .0 ± 2.1	0.21
Complications (n)	9	2	0.085
Discharged (%)			
From SICU	99	100	
From hospital	97	100	
Deaths (%)			0.56
In SICU	1	0	
In hospital	3	0	

Values are mean ± SD unless otherwise noted.

S155

TITLE: DO HISTAMINE H2 BLOCKERS WORK UNDER ANESTHESIA? THE EFFECTS OF RANITIDINE GIVEN INTRAOPERATIVELY ON GASTRIC PH AND VOLUME.

AUTHORS: E.W. Lee, M.D., N.L. Pace, M.D. and J.L. Peters, M.D.

AFFILIATION: University of Utah Department of Anesthesiology, Salt Lake City, Utah, 84132.

INTRODUCTION: Gastric pH and volume have long been recognized as critical factors in the final outcome of pulmonary aspiration. It is well known that histamine H2 antagonists given 60-90 min preoperatively has the desired effect of increasing gastric pH, and in some studies, decreasing gastric volume. For this reason it would be beneficial to determine if histamine H2 antagonists would have the same desired effect if administered under general anesthesia.

This study evaluated the histamine H2 antagonist ranitidine's ability to increase gastric pH and decrease gastric volume under general anesthesia.

METHODS: After Institutional Review Board approval and informed consent was obtained, twenty ASA class I and II patients were divided into two equal groups. A study group received ranitidine 50 mg IV under general anesthesia and a control group received a placebo. The study was double blinded. All cases selected were elective surgical procedures in which the patient was NPO for at least 8 hours and had general anesthesia with endotracheal intubation.

A 18 French Zinetics Graphrobe ST combination gastric pH probe-salem sump (accuracy ± 0.1 pH units) was placed into the stomach. The initial pH was recorded then the gastric contents were aspirated with a Luer slip 60 cc syringe and the volume measured. The gastric contents were discarded and the drug or placebo administered intravenously over a 5 min period. Gastric pH was recorded every 5 min for 90 min after the intravenous infusion. At the end of the 90 min the gastric contents was again measured. Statistical comparisons were performed by unpaired t-tests and alpha was set at 0.05.

RESULTS: Group I was designated the control group. The mean age was 36.1 ± 14.7 years with a mean body weight of 165.5 ± 22.6 pounds. Group II was designated the study group and had a mean age of 47.3 ± 15.8 years with a mean body weight of 152.5 ± 17.8 pounds. The initial gastric pH of Group I ranged from 1.9 to 3.4 with a mean of 2.2 ± 0.45. The initial pH of Group II ranged from 1.8 to 2.4 with a mean of 2.11 ± 0.19 (no statistically significant difference between the groups).

The final pH reached for Group I ranged from 2.3 to 4.8 with a mean of 2.81 ± 0.69 while for Group II the range was from 3.4 to 6.8 with a mean of 5.6 ± 0.96 (statistically significant).

The maximum pH reached in Group I ranged from 2.3 to 4.8 with a mean of 2.8 ± 0.69 while for Group II the range was from 5.0 to 7.0 with a mean of 6.1 ±0.73 (difference, statistically significant).

The time to maximum pH change was significantly different with a range for Group I from 50-99 min (mean 79.4 ± 15.1) versus 20-90 min (mean 58.5 ± 23.2) for Group II.

The time to a change in pH >7.25 was significantly different ($p<0.01$) between Group I, mean 62.6 ± 36 min and Group II mean 19 ±15 min.

The amount of gastric aspirate at the end of 90 min was small and the difference insignificant between the two groups (mean value of 5.9 cc for Group I and 4.1 for Group II).

DISCUSSION: Previous studies of histamine H2 antagonists indicate that when given 60-90 min preoperatively the gastric pH is increased (1-5) and in some studies the gastric volume is decreased (1,2,6). A salem sump determination of gastric volume has been shown to remove all but 4 cc with this method. Our study demonstrates this even if a H2 blocker cannot be administered prior to induction of anesthesia it still may be beneficial to give intravenously after induction for protection during the surgery and at the time of emergence. While gastric volume may not be reduced a pH above 2.5 which occurred in all of our treated patients with ranitidine within 90 min would protect against chemical acid injury during emergence. Since 6 out of 10 of our ranitidine treated patients had a pH change by 10 min during general anesthesia, it may be prudent to give ranitidine immediately prior to induction to minimize the potential consequences should aspiration occur.

REFERENCES:

1) Clin Pharmacol Ther 40:665-672, 1986; 2) Anesth Analg 61:988-992, 1982; 3) Can Anaesth Soc J 28:33-37, 1981; 4) Can Anaesth Soc J 28:29-32, 1981; 5) Anaesthesia 33:775-778, 1978; 6) Acta Anaesth Scand 24:25-30, 1980

S156

Title: OUTPATIENT INTRATHECAL MORPHINE FOR CHRONIC PAIN PATIENTS

Authors: T.L. Lee, M.D., T.J. Lamer, M.D.
Affiliation: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905

Introduction: For patients with cancer-related pain, intrathecal (IT) morphine is a potentially valuable therapy. Routine hospital admission of patients after IT morphine may not be necessary. A retrospective study was performed to test the hypothesis that, in selected patients, IT morphine may be safely administered on an outpatient basis.

Methods: After IRB approval, charts of all patients who received IT morphine as outpatients in the past five years were reviewed. Information about the patient's diagnosis, duration of oral narcotic therapy, side effects of IT morphine, and need for hospitalization were obtained.

Results: IT morphine was administered in 108 outpatient cases. Most patients had a diagnosis of cancer-related pain and were being considered for an implanted subarachnoid morphine pump. All patients were on oral narcotic therapy, the duration varying from one month to four years. IT morphine dose ranged from 0.2 to 2 mg with most patients receiving 1 mg or more. Side effects were seen in 26 cases (Table). Five patients required overnight hospitalization. No patient demonstrated clinical signs of respiratory depression.

Discussion. Previous reports have demonstrated the safe use of outpatient epidural narcotic analgesia in selected patients.(1) Similar data are not available for IT morphine, and many institutions require all patients receiving IT morphine to be monitored in an intensive care unit. This study demonstrated that patients already on oral narcotics appear to show tolerance to respiratory depression from IT morphine. Although the mechanism and time to develop tolerance is not known, it appears that patients with cancer-related pain taking regularly scheduled narcotics for greater than one month may safely undergo diagnostic IT morphine injection as outpatients. The practice of routinely hospitalizing all patients after IT morphine may not be justified.

Table. Side Effects of Intrathecal Morphine
n=108, (age: 61, range 34-88)

	Number of Patients	Number Hospitalized
No side effects	81	0
Nausea & vomiting	18	2
Pruritis	10	0
Urinary retention	6	1
Somnolence/Drowsy	3	2
Headache	1	0

Reference.

1. Pain 16:41, 1983

S157

Title: EMERGENT REINTUBATION IN THE POSTANESTHESIA RECOVERY ROOM
Authors: T.L. Lee, M.D., R.L. Lennon, D.O.
Affiliation: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905

Introduction: Studies have shown that while the incidence of anesthetic mortality has declined, the incidence of complications occurring in the postanesthesia care unit (PACU) remain significant.(1) We performed a retrospective study to evaluate the incidence of and factors leading to emergent intubation in the PACU. We were interested in the role of nondepolarizing muscle relaxants (NDMR) in emergent PACU reintubations.

Methods: After IRB approval, 16,670 anesthetic records over a 6-month period were reviewed. Sixteen patients required emergent reintubation in the PACU. Information about the patient's ASA status, medical history, preop medications, anesthetic agents and all drugs used intraop, duration of anesthesia, time from last NDMR dose to reversal, patient's esophageal temperature at end of case, monitoring of neuromuscular function, and methods used to assess the airway problem leading to intubation were obtained. Standard NDMR dose(2) and standard neostigmine dose (70 μg/kg) were calculated and compared to the actual dose administered.

Results: All 16 patients requiring intubation in the PAR were classified as ASA III. Two patients were excluded from data analysis. (One patient received succinylcholine after neostigmine and the other patient did not receive any drugs intraop.) Nine records indicated a nerve stimulator was used. Four subgroups were identified (see Table). Hypothermia (T ≤ 35°C) occurred in 5/14 patients with one patient's temperature as low as 32.5°C. Renal insufficiency (creat > 2.3) was seen in 3 patients. Greater than the standard dose of NDMR was given in 9/14 patients, with 5 patients receiving more than double the standard dose. Four of these patients were also hypothermic. Twelve of 14 patients were administered less than the standard neostigmine dose for reversal.

Discussion. The study points out important quality assurance concerns. Factors which augment NDMR such as temperature, renal insufficiency, antibiotics and antiarrhythmias must be considered. Airway difficulties are high on the list of differential diagnosis for restlessness and should be evaluated prior to sedative and/or narcotic therapy. It is important to realize that there is a large variability in patient response to all relaxants. Therefore, it is imperative to monitor neuromuscular function to avoid excess NDMR.

Table. Emergent Reintubations in PAR, n = 14

Hypothermia	5
Renal insufficiency	3
Greater than standard dose NDMR	9
Less than standard neostigmine dose	12

References.
1. Can Anaesth Soc J 33:22-31, 1986
2. Anesthesia, RD Miller, 2nd Ed., 1986, p. 897

S158

TITLE: DEXMEDETOMIDINE REDUCES CORTISOL AND β-ENDORPHIN RESPONSES TO INTUBATION AND LAPAROSCOPY
AUTHORS: Lehtinen A-M, M.D., Aho M, M.D., Erkola O, M.D., Korttila K, M.D.
AFFILIATION: Department of Anesthesia, Women's Hospital, SF-00290 Helsinki

Introduction: Surgery and tracheal intubation increase plasma concentrations of cortisol and β-endorphin immunoreactivity (ir β-E)[1]. A novel alpha$_2$-adrenergic agonist, dexmedetomidine has been shown to attenuate the hemodynamic response to laryngoscopy and endotracheal intubation, and diminish the need of isoflurane during surgery[2]. There is evidence in experimental animal models that dexmedetomidine decreases cortisol concentration in basal conditions[3]. The present study was designed to find out whether intramuscular dexmedetomidine premedication attenuates the increase in cortisol or in ir β-E concentration during anesthesia and during gynecologic laparoscopy.

Methods: This double-blind study was approved by the Ethical Committee of the Hospital and comprised 100 consenting healthy women, randomly allocated to five groups, of 20 patients. Every patient was given an intramuscular injection 45-60 min before the induction of anesthesia. Women in study groups received dexmedetomidine 0.6, 1.2 or 2.4$\mu g.kg^{-1}$. For comparison two groups of women were treated either with oxycodone 0.13$mg.kg^{-1}$ or with saline. Plasma cortisol was measured in 100 patients (20 pts in each group), and plasma ir β-E in 20 patients in the control group, and in 20 women receiving dexmedetomidine, 2.4$\mu g \cdot kg^{-1}$. The laparoscopies were performed at 8.00-10.00 a.m., in each case. The blood samples were taken before premedication, before the induction of anesthesia (BI), 5, and 15 min after tracheal intubation, 10 min after the beginning of laparoscopy (SCO), and 1 h after the procedure (REC).

Prior to induction of anesthesia glycopyrrolate 0.2mg and vecuronium 0.6mg were administered. Induction was performed with a fixed dose of thiopental, 4.5$mg.kg^{-1}$, and succinylcholine was given to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane at a standard 0.3% end tidal concentration in 30/70% oxygen-N_2O-mixture. Vecuronium was used to maintain 80% relaxation. Laparoscopy began no sooner than 15 min after the intubation. Kruskall-Wallis analysis, followed by the Mann-Whitney test, was used to compare the changes in plasma cortisol and β-endorphin concentrations between the groups. Within the study groups, significant changes in cortisol and ir β-E concentrations were identified using the Wilcoxon rank sum test.

Results: The plasma concentrations of cortisol, measured just before the induction of anesthesia, were significantly reduced from control values in all groups. At this point, no difference was found between the groups. After laryngoscopy and endotracheal intubation, and also during the laparoscopy, the increase in plasma cortisol was attenuated in women premedicated with 2.4 $\mu g.kg^{-1}$ and oxycodone compared to the saline group (Fig 1). Dexmedetomidine 2.4 $\mu g.kg^{-1}$ similarly attenuated the increase in ir β-E (Fig 1.)

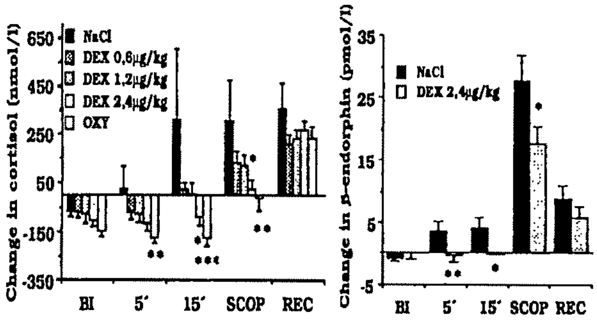


Fig 1. * $P<0.05$, ** $P<0.01$, and *** $P<0.001$ vs saline

Discussion: Based on these preliminary results, intramuscular dexmedetomidine, given 45-60 min preoperatively, appears to attenuate the increase in plasma cortisol and ir β-E concentrations in response to endotracheal intubation and to gynecologic laparoscopy. The ability of dexmedetomidine to reduce the maximal increase in hemodynamic and endocrinologic responses to surgical stress, is comparable to the effects of opioids or a deep level of anesthesia[1,4]. It is not clear, whether the blunting effect of dexmedetomidine simply reflects a deeper level of anesthesia. Our study provides more evidence for a link between the effects of alpha$_2$-agonists and endogenous opioid system. The central mechanisms behind this kind of anesthetic interaction are still only speculative but may represent an interesting area for further investigation[5].

References:
1. Br J Anaesth 56;247-250,1984
2. Anesth Analg (suppl) 70:S5,1990
3. Eur J Pharmacol 183/6:2343-2344,1990
4. Aneshesiology 54:390-399,1981
5. Anesthesiology 72:959-961,1990

S159

Title: SUFENTANIL VS FENTANYL INTRATHECALLY FOR LABOR ANALGESIA

Authors: CH Leicht, M.D., M.P.H., DE Evans, M.D., WJ Durkan, M.D., S Noltner, M.D.
Affiliation: Mayo Clinic, Rochester, MN, and Naval Hospital, San Diego, CA

Introduction: The addition of fentanyl or sufentanil to local anesthetic solutions for labor has allowed for reductions in the concentrations of local anesthetic used; and consequently, reductions in common side effects of local anesthesia, mostly namely hypotension and motor blockade.[1] Intrathecal morphine alone, i.e.; without local anesthetic, has been shown to provide effective analgesia for labor.[2] We recently performed a pilot study using intrathecal sufentanil as the sole analgesic agent for labor with promising results.[3] To corroborate these results, to further evaluate intrathecal sufentanil, and to compare sufentanil with fentanyl administered intrathecally for labor analgesia, we performed the following study in a prospective, double blind, randomized fashion.

Methods: IRB approval and informed consent were obtained. Group I patients were administered 25 mcg of fentanyl intrathecally and group II received sufentanil 10 mcg. All doses were diluted to 1 ml with sterile preservative-free normal saline and administered in the lateral position at L_{2-3} or L_{3-4} interspaces via a 26 gauge spinal needle. A 10 cm visual analogue scale was used to assess pain relief and severity of side effects.

Results: Gravity, parity, height, weight, and cervical dilatation at the time of administration was similar between the two groups. Our results indicate that intrathecal sufentanil is more effective for relief of labor pain and exhibits a more rapid onset than fentanyl. Mean onset of analgesia was faster in the sufentanil group: 12.0 ± 6.7 versus 7.0 ± 4.4 (minutes, mean ± S.D.) in groups 1 and 2, respectively. Pain relief was greater in the sufentanil group; with a 58 ± 16.4% reduction of pain in group I versus a 76 ± 19.5% reduction in group II (mean ± S.D.). Thirty percent of patients who received sufentanil reported complete analgesia whereas no patient who received fentanyl noted complete analgesia. No significant change in blood pressure, pulse, respiratory status or fetal heart tracing was noted at any time in any patient. No patient in either group requested treatment for pruritus or nausea/vomiting. However, 60% of group I and 85% of group II experienced mild transient pruritis lasting from 10 to 60 minutes. No patient experienced a postlumbar puncture headache severe enough to require an epidural blood patch.

Discussion: Our results suggest that intrathecal sufentanil is more effective than intrathecal fentanyl for providing labor analgesia. The onset of which is rapid, the duration is moderate, side effects appear to be very minimal, and risk of motor blockade or hypotension appears absent. Our incidence of postlumbar puncture headache was zero. This may, however, merely be a consequence of the few number of patients studied; or it may be related to the use of intrathecal narcotics as previously suggested.[4] As a single bolus, the duration would appear to be most suitable for multiparous patients, especially those in which a prolonged labor is not anticipated, or primiparous patients who are well into active labor. Additionally, we are currently evaluating intrathecal sufentanil administered by via an indwelling intrathecal catheter, in conjunction with a small amount of local anesthetic, and administered via a PCA device, which may broaden the applicability of this technique.

References: 1) Anesthesiology 71:A842, 1989. 2) Br J Anaesth 56:1351-1359, 1984. 3) Anesthesiology 73:Abstracts, 1990. 4) Anesthesiology 71:A911, 1989.

S160

TITLE: DOES CEREBROVASCULAR HYSTERESIS EXIST UNDER ISOFLURANE ANESTHESIA IN CHILDREN?

AUTHORS: J LEON, MD, B BISSONNETTE, MD,LERMAN J,MD
AFFILIATION: Deptartment of Anaesthesia, Research Institute, Hospital for Sick Children, Univ of Toronto,Toronto,Canada

Isoflurane has lesser cerebral vasodilatory properties as compared to halothane.1 Halothane shows a delay in return to cerebral blood flow (CBF) baseline after 1.5 MAC, a hysteresis phenomena.2 This information is invaluable for the management of children with increased intracranial pressure and during long neurosurgical procedures. The delay in return to baseline of the CBF has not been investigated during the use of isoflurane. Using the transcranial doppler (TCD) we plan to estimate cerebral blood flow and cerebral resistance by using the cerebral blood flow velocity (CBFV) and cerebrovascular resistance index (RI+) as measured by the TCD.

With approval of our Ethics Committee, 13 ASA I and II, fasted and unpremedicated children for elective urological procedures were studied. Anesthesia was induced with thiopental 5mg/kg, fentanyl 2 mcg/kg, and vecuronium 0.1 mg/kg. After the trachea was intubated, anesthesia was maintained with isoflurane, 75% air in O2 and vecuronium 0.05mg/kg. All patients received a continuous caudal or lumbar epidural block performed with 0.25% bupivacaine prior to incision. Ventilation was adjusted to achieve normocarbia. Fresh gas flows were maintained constant throughout the study to avoid any variation in intrathoracic pressure. Normothermia was maintained. Patients, initially, randomly received either 0.5 MAC, 1.0 MAC, and 1.5 MAC I followed by randomized I MAC concentrations in an increasing or decreasing fashion to complete the loop. The time-response effect of isoflurane on CBFV and RI+ was studied in 6 patients. CBFV and RI+ was recorded every 15 minutes for 90-135 minutes. At each isoflurane concentration [I] three measurements of CBFV and RI+ was measured. A time interval of 15 minutes was allowed between [I] changes to achieve steady state. SAP, HR , O2 saturation, end-tidal I, and inspired O2 were recorded. CBFV and RI+ in the Middle Cerebral Artery (MCA) was measured with the TCD. Statistical significance (p<0.05) was determined with paired t-test, ANOVA and the SNK test tor multiple comparisons.

The mean (±S.D.) age and weight was 47.5±31.5 mo and 17.0±4.7 kg. CBFV and RI+ were the same at all MAC increments (fig 1). There was no change in CBFV or RI+ over time in 6 patients (fig 2). HR, SAP, temp, and 02 stauration did not change significantly during the study.

We observed that increasing or decreasing [I] did not modify cerebrovascular circulation in a hysteresis fashion. Previous investigators found that up to 1.5 MAC I had an insignificant effect on cerebral blood flow.3 We eliminated the possible effect of isoflurane solubility on cerebrovascular tone by showing no change in CBFV or RI+ over time. During prolonged surgical procedures, variation of clinical [I] up to 1.5 MAC or constant [I] use will not alter cerebrovascular tone.

We thank MEDASONICS, Canada for providing the TCD.

1.Anesthesiology, 40:A62, 1974. 2.Anesthesiology, 71:A327, 1989.
3. Anesthesiology, 63:391, 1985.

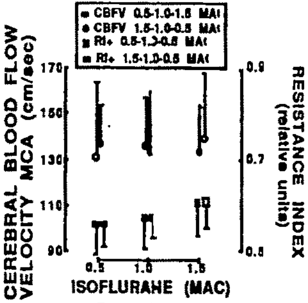


figure 1

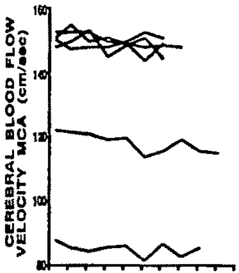


figure 2

S161

TITLE: DOES HALOTHANE AFFECT THE CEREBROVASCULAR RESPONSE TO CARBON DIOXIDE IN ANESTHETIZED CHILDREN?

AUTHORS: J LEON, MD, B BISSONNETTE, MD,LERMAN J,MD
AFFILIATION: Deptartment of Anaesthesia, Research Institute, Hospital for Sick Children, Univ. of Toronto,Toronto, Canada M5G 1X8

Halothane(H) is the most popular inhalational agent in pediatric anesthesia. It is now evident that H causes the most cerebral vasodilation of all the inhalational agents.1 A recent study using transcranial doppler (TCD) in infants and children has shown that when H concentration is decreased there is a delay in return of CBF to baseline, a hysteresis phenomena.2 Studies on the effect of CO2 on CBF have shown that CO2 causes a linear increase in CBF between 20-60 mmHg.3 It is the practice with raised intracranial pressure to use hyperventilation to attenuate any increase in CBF. We designed this study to determine if two different clinical concentrations of H affect the cerebrovascular reactivity to CO2 in anesthetized children.

With approval of our Ethics Committee, 15 ASA I or II children fasted and unpremedicated for elective urological procedures were studied. Anesthesia was induced with thiopentone 5mg/kg, fentanyl 2mcg/kg, and vecuronium 0.1 mg/kg. After the trachea was intubated, anesthesia was maintained with H, 75% air in O2 and vecuronium 0.05mg/kg. All patients received a continuous caudal or lumbar epidural block performed with 0.25% bupivacaine prior to incision. Ventilation was adjusted to achieve an end tidal CO2 (PE'CO2) of 20 mmHg while H equilibrium was being established. Fresh gas flows were maintained constant to avoid any variation in intrathoracic pressure. Normothermia was maintained. Patients were first equilibrated to 0.5 MAC while PE'CO2 was randomly equilibrated to 20, 40, and 60 mmHg with an exogenous source of CO2. After three measurements at each C02 concentration were recorded, the patients received 1.0 MAC H and C02 was randomly assigned as before. A time interval of five minutes was allowed between CO2 changes and fifteen minutes was allowed between H changes to achieve steady-state. SAP, HR, O2 saturation, end-tidal H and inspired O2 were recorded. Cerebral Blood Flow Velocity (CBFV) and resistance index (RI+) in the middle cerebral artery (MCA) was measured with a TCD. CBFV, RI+, and PE'CO2 were analyzed using logarithmic regression and r2 value. Statistical significance (p<0.05) was determined with paired t-test, ANOVA and SNK test for multiple comparisons.

The mean (±S.D.) age and weight was 46.1 ±30.2 mo and 17.0±6.1 kg. The CBFV increased logarithmically as PE'CO2 increased during both 0.5 MAC (r2=0.99) and 1.0 MAC (r2= 0.95) H. The RI+ showed an inverse log relationship with PE'CO2 at 0.5 MAC (r2= 0.99) and 1.0 MAC (r2=0.53) H (fig. 1). There was no significant difference between CBFV at all CO2 levels when comparing 0.5 MAC and 1.0 MAC H, but there was a difference between 20 and 40 and 20 and 60 mmHg CO2 at both 0.5 MAC and 1.0 MAC H (*, p<0.05) (fig. 2). HR, SAP, temp and 02 stauration did not change.

H attenuates cerebrovascular reactivity to CO2. H has been shown to dilate the cerebrovasculature but have a delayed return to baseline upon decreasing the concentration.2 At PE'CO2 of 60 mmHg the arterioles appear to be fully vasodilated since the CBFV is nearly identical at both 0.5 and 1.0 MAC and RI+ seems to have plateaued. There is a partial cerebrovascular response at all CO2 values. Cerebral vasomotor paralysis secondary to H may play a part. If there is no change in the diameter of pediatric basal cerebral vessels with changes in CO2 we can assume that changes in CBFV are proportional to changes in CBF.4 H anesthesia attenuates cerebrovascular reactivity to CO2; one reaches maximal arteriolar vasodilation at normocapnia and hypercapnia.

We thank MEDASONICS, Canada for providing the TCD.

1. Anesthesiology, A62, 1974.
2. Anesthesiology: A327, 1989.
3. J Neurosurgery, 57:769, 1982.
4. Invest Radiol, 2:17, 1967.

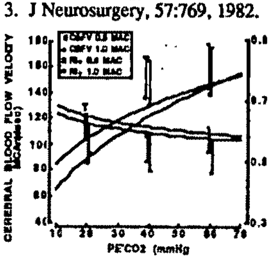


fig 1

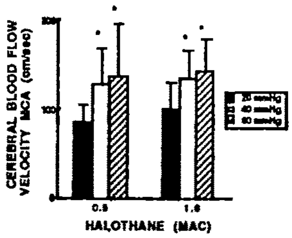


fig 2

S162

Title: DOES ANTIEMETIC PROPHYLAXIS WITH ONDANSETRON PROLONG RECOVERY TIME?

Authors: JB Lessin RN, SS Azad MD, F Rosenblum MD, RR Bartkowski MD PhD, A Marr CRNA
Affiliation: Jefferson Medical College, Department of Anesthesiology, Thomas Jefferson University, Philadelphia, PA 19107

Introduction: Ondansetron (Glaxo), a selective serotonin 3 (5 HT-3) receptor antagonist, is effective in preventing cisplatin induced nausea and vomiting.[1] Other antiemetics are associated with sedation which impairs cognitive function and may delay recovery room discharge. We examined the use of I.V. OND for the prevention of postop nausea and its effect on patient recovery time.

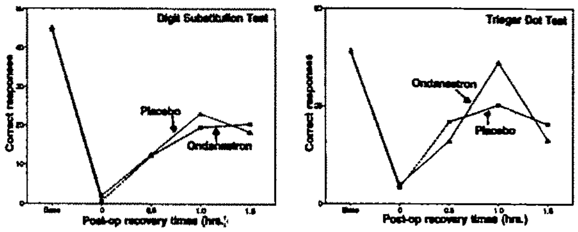
Methods: Fifty ASA I and II female patients scheduled for gynecologic surgery gave informed written consents to participate in this IRB approved study. All patients received diazepam 5-10 mg p.o. 1-2 hours prior to surgery. Patients were randomized to receive either 2 I.V. doses of 8 mg of OND or placebo infused over 2-5 min at 8 hour intervals. Each patient received the first dose within 30 minutes of the start of surgery. A standardized anesthetic was used including narcotic and inhalation agent. Intraop antiemetic and naloxone were avoided. Morphine or meperidine were used in the recovery room to treat pain as needed. Awakening time was measured from N_2O off until patient reponse. Cognitive functions were tested, using the Trieger Dot Test and Digit Substitution Test, preop and every half hour postop until discharge from the recovery room. ANOVA for repeated measures and T tests were used to analyze data. Significance was p<.05.

Results: There were no significant differences between the groups in age, height or weight. Patients in both treatment groups demonstrated similar improvement in Trieger Dot Test and Digit Substitution Test (Figure 1). Although not significantly different, more patients in the OND group were able to perform the Digit Substitution and Trieger Dot Tests postoperatively. Awakening times were similar in both groups (OND 5 ± 3 min, P 9 ± 10 min, NS). The length of time spent in the recovery room was similar in both groups (OND 94 ± 33 min, P 94 ± 31 min, NS).

Discussion: We have shown elsewhere that OND is an effective antiemetic. Side effects associated with common postop antiemetic therapy, such as sedation, dysphoria and other extrapyramidal effects that may prolong a patient's recovery period, were not demonstrated by patients receiving OND. Patients in both groups were equally awake and responsive postop. Ondansetron is a promising alternative to current antiemetic therapy.

References:
1. NEJM, 322(12), p 810, 1990.

Figure 1.



S163

Title: Long-term Recovery: Desflurane vs Propofol

Authors: JL Lichtor, MD, JL Apfelbaum, MD, B Lane, BS, D Coalson, MD, A Uitvlugt, MD, G Rupani, MD, B Schreider, MD, PhD, B Glosten, MD, MF Roizen, MD, R Finn, MD
Affiliation: Department of Anesthesia & Critical Care, University of Chicago, Chicago, IL (Supported in part by Anaquest)

Introduction: In an initial study in animals, recovery after desflurane compared with recovery after other inhalation agents was rapid.[1] We sought to compare long-term psychomotor recovery after desflurane or propofol anesthesia in humans.

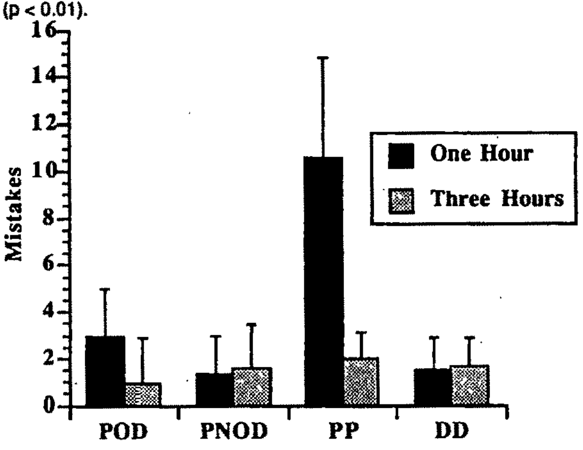
Methods: With permission from our IRB and after informed consent, four different one-hour general anesthetics were administered randomly to volunteers: induction with propofol followed by O_2/desflurane, O_2/N_2O/desflurane, or propofol infusion O_2/N_2O for maintenance; or induction with desflurane followed by O_2/desflurane maintenance. There was a one-week wash out period between treatments. Anesthesia maintenance was titrated to clinical effect so that blood pressure was within 20% of baseline and the volunteers did not move. Before and 1 and 3 hours after anesthesia, the following psychomotor tests were administered: Digit Symbol Substitution Test (DSST)–match letters to symbols; Short Term Memory Test (STM)--recall words; Action Judgment Test (AJ)--driving test where markers must be avoided; Maddox Wing (MW)–tests eso/exophoria. Repeated measures analysis of variance was used to assess drug and time effects after anesthesia.

Results: In all groups for which desflurane was used for maintenance, psychomotor performance (DSST, STM, AJ, MW) 1 hour after anesthesia surpassed that of the groups who received propofol maintenance (STM, AJ, and MW, $p < 0.01$; DSST, $p < 0.025$). Three hours after anesthesia, performance overall was not different from that at baseline (fig).

Discussion: Although psychomotor performance in volunteers recovered rapidly after propofol infusion for one hour, recovery after desflurane was even more rapid, suggesting that desflurane may be very advantageous for ambulatory surgery. Future studies are needed to determine the cost-effectiveness of desflurane compared to that of propofol or isoflurane for ambulatory surgery.

Reference: Anesth Analg 66:977-982, 1987

Figure. Action Judgment Test: Mean increase in mistakes (± SEM) 1 and 3 hours after the end of anesthesia compared to baseline. **POD**-propofol/O_2/desflurane; **PNOD**-propofol/N_2O/desflurane; **PP**-propofol/propofol; **DD**-desflurane/desflurane. One hour after anesthesia, mistakes after propofol infusion were significantly more frequent than mistakes after anesthesia maintained with desflurane ($p < 0.01$).



S164

TITLE: TRANSDERMAL NITROGLYCERIN DOES NOT REDUCE THE INCIDENCE OF PREBYPASS ISCHEMIA IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

AUTHORS: MG Licina MD, NJ Starr MD, FG Estafanous MD, CE Smith MD, JM Blum MS, M Bednarski RN

AFFILIATION: Department of Cardiothoracic Anesthesia, Cleveland Clinic, Cleveland OH 44195

Incidence: The role of prophylactic application of transdermal nitroglycerin (NTG) in preventing or diminishing the incidence of myocardial ischemia in patients undergoing coronary artery bypass artery surgery (CABG) was examined. Previously it has been reported that during CABG, 18-78% of patients develop ECG evidence of myocardial ischemia associated with a 3 fold increase of perioperative myocardial infarction (PMI).[1] Prophylactic NTG infusion has had varied effects on myocardial ischemia and PMI patients with angina undergoing anesthesia.[2-4]

Methods: Following institutional approval, 103 CABG patients were entered into a randomized double blind study. 5 mg transdermal NTG (50 patients) or placebo (53 patients) was applied at the same time preop medications were given: morphine sulfate .1mg/Kg and scopolamine 0.4 mg. All patients had pulmonary artery catheters. Continuous ECG ST segment analysis of leads I, II, V5 were recorded via a Marquette Series 7000 ECG monitor. ECG and hemodynamics were collected and analyzed at five points prior to cardiopulmonary bypass: 1) arrival to the OR, 2) and 3) 3 and 10 minute post intubation 4) at sternotomy and 5) at aortic dissection. In addition if ECG ST segments at anytime were >= 0.1 mV then a complete hemodynamic profile was obtained and therapy instituted. Anesthesia was induced with fentanyl 40 ug/Kg and oxygen. Maintenance of anesthesia was with fentanyl up to 75 ug/Kg, valium up to 0.2 mg/Kg and enflurane 0-.75%. Muscle relaxation was obtained with pancuronium and metocurane in a dosage ratio of 1:4. Analysis of results was by univariate analysis using chi-square or Fischer's two tailed test. Continuous variables were analyzed by student t test.

Results: Between the placebo and NTG groups there was no difference in age, gender, reoperation rate, moderate or severe preoperative left ventricular function, hypertension, diabetes, previous MI or the use of beta and calcium channel blocker. Overall intraoperative hemodynamics were similar between the 2 groups. 7 patients in the placebo group (13.2%) had episodes of myocardial ischemia and 6 patients in the NTG group (12%) had episodes of myocardial ischemia. Of the ischemic patients, 2 of the 7 placebo patients had a PMI (one of which was incompletely revascularized) and 0/6 in the NTG group had a PMI. Unlike the comparison between the overall placebo versus control group, within the ischemic patients of 13 only 1was on beta blocker whereas 11 of 13 were on calcium channel blockers.

Discussion: NTG is frequently used as part of the premedication for patients undergoing CABG operations throughout the world. NTG used in this fashion was thought to decrease the incidence of prebypass ischemia and thus PMI.

The double blinded clinical study does not support the use of prophylactic use of transdermal nitroglycerin; but further research is needed to delineate the role of perioperative beta blockers to reduce the incidence of ischemia in CABG patients.

Reference: 1) Anes 65:539-542, 1986. 2) Anes 64:785-789,1986. 3) Anes 61:385-393, 1984. 4) Anes 62:107-114, 1985. 5) Anes 61:193-196, 1984.

S165

Title: **Another Application of Transesophageal Echocardiography—Aortic Annulus Measurement**

Authors: C. Y. Lin, M.D., C. Theo, M.D., R. Finn, M.D., S. Aronson, M.D., R. Karp, M.D., Ming-Wen Yang, M.D.
Affiliation: Departs of Anesthesia and Critical Care and Surgery, University of Chicago, Chicago, IL

Introduction: Transesophageal echocardiography has become a relatively common monitor in recent years. It is valuable for the assessment of valve morphology and valve functional status and provides a means to evaluate wall motion abnormalities in patients with poor ventricular function and to detect ischemia perioperatively for better management. With recent improvements in allograft procurement and storage techniques, interest in the use of allografts for aortic valve replacement has been renewed. "Cryo" preserved allografts usually require 20-30 min to thaw following careful sizing of the valvular annulus. This 20-30 min period normally takes place following initiation of cardiopulmonary bypass and aortic cross-clamping. In an attempt to reduce the duration of ischemic arrest, we compared the measurement of aortic annulus obtained before bypass with transesophageal two-dimensional echocardiography (2-D TEE) with measurement obtained through the placement of a dilator of known diameter through the annulus.

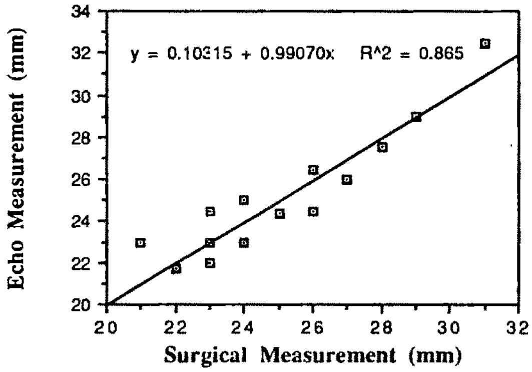
Method: Following Institutional Review Board approval, 18 patients scheduled to receive aortic allograft replacement were studied. Following high dose fentanyl anesthesia, a 2-D TEE transducer (GE RT 5000) was placed in the esophagus. Before cardiopulmonary bypass was started, the annulus was measured during several different cardiac cycles. This measurement was compared with the direct surgical measurement obtained following cardiopulmonary bypass during aortic cross-clamping.

Results: There was no significant difference when measurement of annulus by 2-D TEE was compared with measurement surgically (fig).

Discussion: Freehand aortic allograft valve replacement is a complex procedure that requires careful sizing and insertion without frame. That we were able to obtain accurate measurements by 2-D TEE intraoperatively in this study suggests that 30 or more minutes of waiting time for thawing following aortic cross-clamping can be saved. The use of 2-D TEE can aid correct allograft valve measurement and reduce aortic cross-clamping time.

References:

1. J Thorac Cardiovasc Surg 94:812, 1987
2. J Cardiac Surg 3:69, 1988.



S166

TITLE: USING A HEAD COVERING OF T-727 THERMAL FABRIC TO CONSERVE CORE BODY TEMPERATURE DURING ANESTHESIA

AUTHORS: L. E. Mac Donald, M.S.N., C. Franklin, M.D., Elanda Wiseman, Ed.D.
AFFILIATION: Dept. Anesth, Kaiser Foundation Hospitals, Los Angeles, CA 90027

Introduction: Hypothermia is a frequent complication of surgery with general anesthesia. It occurs in 77% of general surgical patients.[1] Hypothermia affects the pharmacodynamics and pharmacokinetics of drugs routinely used during anesthesia.[2] Even more importantly, a patient that is hypothermic postoperatively may have an increase in o_2 consumption and demand 300% above normal which has been shown to significantly increase postoperative morbidity and mortality.[1,3] This study compared the effectiveness of a T-727 thermal hat to a cotton towel head covering in conserving core body temperature of persons undergoing lower abdominal surgery with general anesthesia.

Methods: The protocol was approved by the Foundation's Institutional Review Committee and informed consent was not required. 50 person, ASA I-III, were randomized into two groups, group A receiving a cotton towel head covering and group B a T-727 hat. Independent variables were either controlled or documented. After induction, core body temperature was measured via esophageal stethoscope immediately and every 15 minutes until emergence.

Results: There were no significant differences between the control and study groups in independent variables with the exception of intraoperative fluid replacement. Group A received a mean of 1.97 L. compared to 1.47 L. for group B ($p < 0.01$). Group B had significantly higher core temperatures than group A at 75 and 120 minutes post induction ($p = 0.047$ and $p = 0.009$). Also, group B had significantly fewer episodes of intraoperative and postoperative complications ($p = 0.007$) than group A (Table 1).

Discussion: The results of this study demonstrated that a head covering of T-727 thermal fabric maintained a significantly higher core body temperature at times during surgery as compared to a cotton towel. Wilkerson found that 1/3 to 1/2 of body heat loss can occur from an unprotected head.[4] The simple step of covering the head with a thermal fabric might decrease surgical and anesthesia complications and lower postoperative morbidity and mortality.

References: [1]Amer Jour of Surg 149:495-501. [2]Surgery 60:85-92. [3]Jour of Clin Pharm 28:860-864. [4]Wilkerson, J. A. (1982). Hypothermia and frostbite.

TABLE 1. LIST OF INTRAOPERATIVE AND POSTOPERATIVE COMPLICATIONS

	Group A	Group B
Shivering	7	2
Arrhythmia	1	1
Unable to extubate	3	0
Hemorrhage	2	0
Hypertension	3	0
Tachycardia	1	0
Hypotension	0	1
Total	17	4

S167

TITLE: MENTAL RECOVERY PARAMETERS AFTER PROLONGED ANESTHESIA WITH PROPOFOL VS. ISOFLURANE

AUTHORS: M.E. Mahla, M.D., A.G. Pashayan, M.D., B.L. Grundy, M.D., S. Mixson, L.P.N., R. Richards, R.Ep.T., A.L. Day, M.D.
AFFILIATION: Depts. of Anesth. and Neurosurg., Univ. of Florida, Gainesville, FL. 32610-0254

ASA class I, II, or III patients (n = 31, 18 to 85 yrs) undergoing lumbar surgery were studied to collect clinical data about recovery from prolonged anesthesia (180-840 min) using propofol.

With institutional approval, following premedication with meperidine and hydroxyzine, patients were randomly assigned to 1 of 3 groups according to the type of anesthetic administered. All 3 groups received sufentanil (up to 0.5 mcg/kg) before administration of the induction agent, and vecuronium (0.1 mg/kg) after induction to facilitate intubation. No further relaxant was given. Group I received propofol (1.02-.5 mg/kg) for induction followed immediately by a variable rate infusion (mean ± SD = 0.08 ± .03 mg/kg/min), a constant rate sufentanil infusion (0.1 mcg/kg/hr), and N_2O, (60-70% end-tidal concentration). Group II received propofol for induction as in group I, a variable rate propofol infusion (mean ± SD = 0.10 ± .04 mg/kg/min) and a variable rate sufentanil infusion (mean ± SD = 0.13 ± .01 mcg/kg/hr). Group III received a thiopental induction, then isoflurane and N_2O, 60-70% endtidal concentration, and a sufentanil infusion as in group I. Variable rate infusions and isoflurane were titrated to clinical needs. Infusions and isoflurane were discontinued at the beginning of skin closure. N_2O was discontinued just prior to turning the patient supine. Controlled ventilation was continued until the patient followed simple commands. Recovery parameters were calculated as time after stopping infusions and included time to following commands, and time to orientation to person, date of birth, and place. Also, mini-mental state exams were performed 1 day prior to surgery, at recovery room discharge, and 24h postoperatively. The 3 groups were not different with respect to severity of operation, duration of anesthesia, age, weight, sex, or ASA class.

The results are summarized in the Table. There were no significant differences in mini-mental state test scores pre- or postoperatively between groups.

Recovery of mental function after prolonged anesthesia was as good or better in the 2 groups receiving propofol than in the group receiving isoflurane/nitrous oxide.

Table. Recovery parameters (values are minutes ± S.D.).

Group	(n)	Follows Command	Oriented x 3
I	8	17.1 (8.1)	27.6 (19.5)
II	13	10.2 (5.9)	18.1 (9.8)
III	10	17.6 (7.5)*	24.5 (12.6)

*$p < .05$ group 2 compared to 3, (Kruskal-Wallis)

S168

Title: ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH THE PRONE POSITION A PILOT STUDY

Authors: D. Mangar, M.D., H. de Sousa, M.D., E. Camporesi, M.D.
Affiliation: Dept. of Anesthesiology, SUNY HSC, Syracuse, NY

Introduction: During surgical procedures requiring patient placement in the prone position, worrisome ECG changes commonly occur, causing confusion for the anesthesiologist. Although this finding is mentioned in anesthesia texts,1,2, no investigations have been reported. We studied the occurance and significance of this phenomenon in a healthy, unmedicated population.

Methods: After IRB approval, 12 ASA Status 1 volunteers gave informed consent. Twelve lead ECGs were obtained in the supine position. Each subject was then turned to prone and the procedure repeated. ECGs were interpreted both by a computer (MAC PC, Marquette Electronics Inc.) and, in a blinded manner, by a trained physician.

Results: All ECGs recorded in the supine position were read as normal. The computer interpreted three ECGs obtained in the prone position as having ischemic changes. However, the physician interpreted these as axial rather than ischemic changes.

Discussion: Our subjects were healthy, unanesthetized and breathed spontaneously, yet 25% of them had EKG changes in the prone position that may have been interpreted as ischemic changes. We have often seen ECG changes after turning anesthetized patients, and with a 3 or 5 lead electrograph, such changes were not easily distinguished from axial changes. It may be useful to investigate the ECGs of patients during surgery in a variety of positions and types of anesthesia to determine the incidence of changes and if they are of any significance.

References:
1. Atkinson RS, G.B. Rushman, J.A. Lee: A Synopsis of Anaesthesia, 10th ed. Wright, Briston, 1987. p 803.
2. Rollason WN: Electrocardiography for the Anaesthetist, 4th ed.. Blackwell Scientific Publication, 1980. P 115-118.

S169

TITLE: ANESTHESIA FOR INTERVENTIONAL NEURORADIOLOGY

AUTHORS: PH Manninen,MD, EA Gignac,MD, AW Gelb,MB,ChB
AFFILIATION: Department of Anaesthesia, University Hospital,
London, Ontario, Canada N6A 5A5

Introduction: During intracranial interventional radiology such as the embolization of arterial venous malformation (AVM) or the balloon occlusion of aneurysms, the risk of potentially disastrous complications is high. The purpose of this study was to review the anesthetic management of these patients, the occurrence and treatment of acute complications.

Methods: After institutional approval, the charts of all patients undergoing interventional radiology during a 12 month period were retrospectively reviewed. Data collected included the anesthetic management during the procedure and the complications related to the anesthetic or to the radiological procedure.

Results: We reviewed the charts of 31 patients who underwent 52 separate procedures as many patients required multiple procedures (Table). The mean (± SD) age of the patients was 42±18 (16 female, 15 male). Four procedures were done under general anesthesia (3 paediatric; 1 giant AVM). Twenty nine procedures were done with neurolept anesthesia using benzodiazepine (midazolam or diazepam), a narcotic (fentanyl, sufentanil, alfentanil or morphine), droperidol and/or dimenhydrinate. Monitors used included an electrocardiogram, automated blood pressure cuff, and pulse oximetry. Neurological assessment of the patient was performed throughout the procedure. Nineteen procedures had no anesthesia coverage, though sedation with fentanyl and valium was given by the radiologist. None of the patients suffered an anesthetic complication. Seven radiological complications occurred (bleeding 4, balloon migration 2, stuck catheter 1). One patient had a severe bleed from an AVM with sudden loss of consciousness requiring intubation, hyperventilation and urgent craniotomy. The patient with the stuck catheter required emergency surgery. Four patients had surgery at an elective time.

Lesion	Number of Patients	Number of Procedures
AVM	15	33
Aneurysm	8	8
Fistula	7	10
Tumor	1	1

Discussion: With the recent advances in interventional neurovascular techniques, many patients with intracranial vascular pathology will have these radiological procedures as either their complete treatment or in preparation for surgical excision.[1] The potential for complications is high. Neurolept anesthesia is the ideal method of sedation, allowing for close neurological monitoring of the patient. We found no complications as a result of our anesthetic management of the patients. The most important role of the anesthesiologist is in the acute treatment of patients who suddenly deteriorate from a complication of the procedure.

Reference: 1. J Neurosurg 56:615-627, 1982.

S170

TITLE: Can Steroids Decrease CPK-MB Levels in CABG Patients?

AUTHORS: A.M. Mantia, MD, J.N. Robinson, MD,
B.B. Myers, MS IV, E.H. Stullken, Jr., MD
AFFILIATION: Department of Anesthesiology, The
Western Pennsylvania Hospital,
Pittsburgh, Pennsylvania 15224 and The
University of Pittsburgh School of
Medicine, Pittsburgh, Pennsylvania 15261

Introduction: Post-induction single bolus high-dose methylprednisolone sodium succinate (MPSS) is used in coronary artery bypass grafting (CABG) procedures to promote cardiac preservation. To assess the efficacy of MPSS in cardiac preservation, we obtained serial preoperative and postoperative CPK-MB levels in CABG patients both receiving and not receiving single bolus high-dose steroids (methylprednisolone).

Methods: Following Institutional Review Board approval, from December 1985 until November 1988, 186 consecutive patients scheduled for routine CABG surgery had pre- and postoperative screening for CPK-MB levels. Sixty-four (64) of the 186 patients received 2 grams of MPSS immediately after induction. CPK-MB levels were measured preoperatively one hour after entry into the ICU, 24, and 48 hours postoperatively. Patients found to have documented myocardial infarctions (increased CPK-MB and new Q-waves on the EKG) were excluded from the study.

Results: Review of Table 1 shows two separate populations: Group 1 (30 CABG x 2 patients and 34 CABG x 3 patients) all received a 2 gram bolus of MPSS after induction of anesthesia. Group 2 (76 CABG x 2 patients and 46 CABG x 3 patients) did not receive any MPSS. For these groups, no significant difference in CPK-MB levels were found between the treated and untreated subjects for either group.

Discussion: Review of our results in Table 1 reveals that the use of MPSS for purposes of myocardial preservation is not warranted solely on the basis of reduced CPK-MB levels. Although some positive effects may be derived from steroid administration (cerebral protection and diminished allergic response), in our study post-induction MPSS did not result in any statistically significant reduction in CPK-MB levels versus controls.

Table 1

24-HOUR CPK-MB*

	No MPSS (Avg ± SD) (n = 122)	2gm MPSS (Avg ± SD) (n = 64)
CABG X 2	6.84 ± 8.04 (n = 76)	6.66 ± 6.33 (n = 30)
CABG X 3	6.72 ± 6.19 (n = 46)	6.19 ± 5.14 (n = 34)

*Normal Range: 0.0 - 3.7 normalized CPK units

MPSS = Methylprednisolone sodium succinate

S171

Title: INSPIRATORY EFFORT IS A SENSITIVE GUIDE TO ANESTHETIC DEPTH

Authors: Randall L. Martin, M.D., Wendell C. Stevens, M.D.
Affiliation: Anesthesia Department, Oregon Health Sciences University, Portland, Oregon 97201

The titration of potent inhalational agents to clinical signs is important during the stimulus-response relationship that exists intraoperatively to avoid sympathetically mediated stimulation or hemodynamic depression. Changes in some clinical signs during surgical stimulation can indicate the depth and adequacy of potent inhalational agents. Factors such as age, debilitation, medications, and pre-medicants can modify the expression of clinical signs during inhalational anesthetics. Inspiratory effort (IE) detected from the capnograph even in the presence of neuromuscular blockade may be an indicator of depth of anesthesia that can be used as a clinical sign to increase or decrease anesthetic delivery. The purpose of this study was to compare the sensitivity of IE and other clinical signs as guides to the titration of enflurane in response to surgical stimulation(1).

Methods: Study methods were approved by our IRB. Twenty-four unpremedicated patients with an average age of 35 years were anesthetized with thiopental 4-6 mg.kg^{-1} IV, FE-N_2O 50% and enflurane (ENF) to 1.25 total MAC while clinical signs and inspiratory effort were recorded during ongoing anesthesia. FA-ENF was adjusted upward or downward in response to clinical need. N-M blockade to a level of one twitch on train of four was obtained with vecuronium infusion to facilitate surgery and to allow control of ET-pCO_2 at 30-38 mmHg. Clinical signs recorded were systolic, diastolic, and mean blood pressure, heart rate, peak airway pressure, IE, pupil size, reactivity, and position, tearing, sweating, breath sounds, and swallowing or movement. Changes in clinical signs from baseline values were analyzed as alveolar ENF concentration was decreased or increased by 10% at 15 minute intervals.

Results: Thirty occurrences of breathing occurred (20 of 24 patients). Spontaneous IE occurred 27 of 30 times when ENF was decreased ($p \leq .001$). Breathing stopped in 20 of 24 instances when ENF was increased ($p \leq .01$). Changes in other clinical signs were statistically insignificant with the exception of decreasing pupillary light responsiveness and tearing which correlated with increasing depth of ENF ($p = .02$).

Discussion: IE consistently occurred with decreasing ENF and ceased with increasing ENF during steady states of N-M blockade and eucapnea intraoperatively. Other clinical signs changed less consistently than IE. IE occurring during inhalational anesthesia in healthy patients was a more sensitive indicator and clinical sign of the anesthetic requirement-surgical stimulation relationship than the other signs we used.

References:

1. Anesthesiol 36:21, 1972.

S172

Title: PHARMACOKINETICS AND PHARMACODYNAMICS OF PIPECURONIUM IN ELDERLY SURGICAL PATIENTS

Authors: RS Matteo MD, AE Schwartz MD, E Ornstein PhD, MD, S Jamdar PhD, J Diaz, H Rodrigues BS*, M Weinberger PhD*
Affiliation: Dept. of Anesthesiology, Columbia U., New York, NY and *Organon Inc., West Orange, NJ

Pipecuronium bromide is a new, long-acting, non-depolarizing muscle relaxant closely related to pancuronium but free of cardiovascular side effects. Since the duration of action of the currently available long-acting non-depolarizing muscle relaxants appears prolonged in the elderly (1-3), this study was undertaken to define the kinetics and dynamics of pipecuronium in elderly surgical patients.

After obtaining institutional approval and informed consent, 9 young (27-59 yrs) and 10 elderly patients (70-82 yrs) were studied. General anesthesia was induced with fentanyl and thiopental and then maintained with N_2O-O_2 (70-30%) and fentanyl by continuous infusion. Muscle responses to supramaximal stimulation of the ulnar nerve at the wrist (frequency 0.1 Hz, duration 0.2 m.s.) were recorded. Pipecuronium 70 µg/kg was given IV, the patients intubated and timed samples of arterial blood were obtained up to 360 min. The plasma was analyzed for pipecuronium by gas chromatography.

Return of twitch heights and recovery indexes were recorded. Plasma concentration-time curves for each patient were generated and used to obtain the kinetic parameters. Comparisons were made between the young and elderly groups by Student's t-test (two-tailed). $P<0.05$ was considered significant. The linear portion of the log plasma concentration-response curves between 20 and 80% paralysis for the two groups were compared by analysis of covariance.

There was no significant difference between the younger controls and the elderly groups for any of the pharmacokinetic or pharmacodynamic parameters (Table). In addition, the slope and intercept of the log plasma concentration-response lines for the two groups were not significantly different.

It has been clearly established in both man (4) and animals (5) that the kidney is the primary organ of elimination for pipecuronium. Furthermore, it is well accepted that renal function normally declines with increasing age. Thus, the finding of this study that the elimination and action of pipecuronium is not affected by age is unexpected.

Rupp (6), however, studied 6 elderly patients given pancuronium and reported that this group did not vary significantly from a younger control group in either kinetics or dynamics. He believed that he was unable to detect significant differences between the two groups because his elderly group comprised "healthy" individuals with presumably good renal function. This may be the explanation for the results of our study since the ability of patients in end stage renal failure to eliminate pipecuronium is clearly impaired, as demonstrated by a prolonged duration of action, a significantly reduced plasma clearance and a prolonged elimination half-life in these patients (4).

The fact that the action, distribution and elimination of pipecuronium is unchanged by increasing age suggests that this drug may be the long-acting relaxant of choice in the elderly.

References:

1. *Anesthesiology* 1982;56:36-40.
2. *Br J Anaesth* 1984; 56:465-71.
3. *Anesth Analg* 1985;64:23-9.
4. *Anesthesiology* 1989;70:7-12.
5. *Anesthesiology* 1989;71:919-22.
6. *Anesthesiology* 1987;76:45-9.

Table: Pipecuronium Kinetics and Dynamics (Mean ± SD)

	Young n=9	*Elderly n=10*	*P*
t1/2 elim (min)	113.6 ± 35	122.3 ± 33	0.584
Clp (ml · kg^{-1} min^{-1})	2.6 ± 0.6	2.7 ± 0.5	0.788
V_1 (ml · kg^{-1})	81.7 ± 41	86.2 ± 19	0.756
Vd area (ml · kg^{-1})	416.9 ± 128	433.0 ± 57	0.723
T 50% recovery (min)	101.0 ± 40	93.0 ± 42	0.686
T 25-75% recovery (min)	49.0 ± 17	62.0 ± 41	0.432

S173

TITLE: EFFECTS OF VOLATILE ANESTHETICS ON ANTIGEN-SPECIFIC T-CELL IMMUNE RESPONSES

AUTHORS: PM MAURER, MD, JL GRUN, PH.D, M TORJMAN M.Ed, H SCHIEREN, PH.D, PH MAURER, PH.D, JL SELTZER, MD
AFFILIATIONS: DEPARTMENTS OF ANESTHESIOLOGY AND BIOCHEMISTRY, JEFFERSON MEDICAL COLLEGE, THOMAS JEFFERSON UNIVERSITY, PHILADELPHIA, PENNSYLVANIA

Introduction: Previous investigations have documented effects of anesthetics on human immune functions[1,2]. There have been no reports examining the effects of volatile anesthetics on the activation of T-cells by specific antigens or cytokines. The availability of a well-characterized murine, antigen-specific T-cell line allowed the detailed study of proliferative[3] and cytokine[4] responses in the presence of halothane and isoflurane.

Methods: A continuous flow system was designed to deliver 100% humidified gas (5% CO_2/95% air) to cell cultures at 37°C. T-cells were cultured with GLA, a synthetic polymer antigen, or cytokines, in the presence or absence of X-irradiated, syngeneic, antigen-presenting spleen cells (APC). The cell cultures were exposed to vaporized halothane or isoflurane for 6-24 hrs, then incubated (5% CO_2/95% air, 37°C) for 2-3 days. The anesthetics were monitored by infrared analysis. Proliferation was assayed by colorimetric MTT reduction[5] and measured by spectrophotometry. Endogenous cytokine (IL-4) production by GLA-stimulated T-cells was determined utilizing a bioassay[6].

Results and Discussion: Both halothane and isoflurane inhibited antigen-specific T-cell proliferation (Fig.1) and endogenous cytokine secretion (Fig.2). The inhibition is dependent upon volatile agent concentration and duration of exposure. The observed phenomenon is attenuated at increased antigen dose. This suggests that anesthetics alter saturable, membrane-based events required for activation of the immune response. Exogenous IL-2 stimulation was inhibited at 24 hrs, but not at 6 hrs of exposure (Table). Isoflurane inhibited the exogenous IL-2 activation to a greater extent than halothane. This indicates discrete effects of these agents on the cellular subpopulations involved in the immune response. Volatile anesthetic inhibition of the immune response provides insight into anesthetic actions at the cellular level. The extrapolation of these results to humans could lead to the design of anesthetic regimens to achieve clinically appropriate immunomodulation.

Figure 1

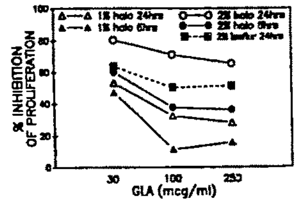
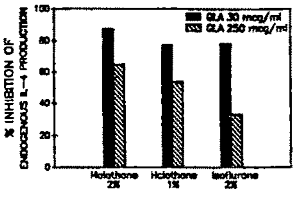


Figure 2



Table

Concentration	Halothane 2%		Halothane 1%		Isoflurane 2%
Exposure (hrs)	24	6	24	6	24
Exogenous IL-2 * (150 units/cc)	27	0	16.6	0	41.4

* Supernatants from ConA treated rat spleen cells added to T-cells + APC

References
1. Anesthesiology 36:206-212, 1972.
2. J Immune Meth 88:277-283, 1986.
3. Immune Letters 16:291-296, 1987.
4. Cell Immunol 29 (In press) 1990.
5. J Immuno Meth 65:55-63, 1983.
6. J Exp Med 166:1229-1247, 1987.

S174

Title: INTUBATION WITH LOW DOSE ATRACURIUM AND VECURONIUM IN INFANTS AND CHILDREN

Authors: D. McGregor, M.D., J. Bires, M.D., R. Lennon, D.O.
Affiliation: Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905

Introduction. With usual intubating doses of vecuronium and atracurium, neuromuscular blockade is reversible in 20 to 30 min in children. For shorter duration procedures requiring a secure airway, intubation is frequently accomplished using succinylcholine or a deep level of volatile anesthetic. The elective use of succinylcholine in pediatric anesthesia remains a controversial issue. Intubation under a deep level of inhalation agent may be complicated by cardiorespiratory depression and/or laryngospasm. In this study, we looked at intubation with low dose atracurium and vecuronium as an alternative to the use of succinylcholine or deep volatile agent in procedures of short duration.

Methods. With IRB approval, forty pediatric patients, physical status I or II, ages 2 mo-8 y were included in the study. Anesthesia was induced and maintained with 30% O_2, 70% N_2O, and halothane. Neuromuscular function was monitored with a Puritan-Bennett relaxograph. Once IV access was secured, the patient received 20 µg/kg atropine and 0.25 mg/kg atracurium or 0.05 mg/kg vecuronium. Intubation time was defined as the time from relaxant administration until the T_1 achieved a value < 25% of control. Time to spontaneous recovery of neuromuscular function was noted by return of T_1 in patients in whom complete neuromuscular paralysis was achieved or the time to reach maximum depression of neuromuscular function in patients in whom only partial paralysis was achieved by relaxant administration.

Results. The results are summarized in the table below.

Neuromuscular Relaxant	# patients	Age	Time to intubation (minutes) mean ± SEM	Time to spontaneous recovery (minutes) mean ± SEM
Atracurium	10	2-12 mo	1.9 ± 0.2†	8.4 ± 1.3
	8♦	13 mo - 8 y	3.4 ± 0.4†	8.1 ± 0.7
Vecuronium	10	2-12 mo	1.4 ± 0.1*	11.5 ± 1.6§
	7♦	13 mo - 7 y	3.2 ± 0.5*	7.3 ± 0.4§

** $p < 0.01$ by unpaired two-tailed t-test; § $p < 0.05$ by unpaired two-tailed t-test; † $p < 0.01$ by unpaired two-tailed t-test; ♦ 2 of 10 patients in the atracurium group and 3 of 10 patients in the vecuronium group did not reach $T_1 < 25\%$ of control after a single dose of relaxant*

Discussion. In patients ≤ 12 mo of age, intubation with low dose atracurium or vecuronium was rapid and the neuromuscular blockade was reversible in a short period of time. Attempted intubation with low dose atracurium or vecuronium in patients ages ≥ 13 mo required a significantly longer period of time than did the infant group, and adequate intubating conditions (T_1 < 25% of control) were obtained in only 70 to 80% of patients. It is not surprising that intubation is more rapid in the infant group since the ED_{50} of both atracurium and vecuronium is known to be lower in infants when compared with children.[1] We suggest that low dose atracurium or vecuronium is a reasonable alternative to intubation with succinylcholine or deep inhalation anesthesia in patients ≤ 12 mo of age who are undergoing elective procedures of short duration.

Reference. 1. Anesthesiology 61:444-453, 1984

S175

TITLE: PERIOPERATIVE THERMAL INSULATION

Authors: JP McGuire and DI Sessler, M.D.
Affiliation: Department of Anesthesia, UCSF, CA, 94143

In the perianesthetic period, cutaneous heat loss comprises ≈90% of total body heat loss (respiratory loss is usually unimportant). We therefore measured cutanous heat loss in volunteers draped with a variety of common perioperative covers.

With IRB approval, we tested 6 insulating materials in each of 5 unanesthetized volunteers minimally clothed in an ≈21°C environment. The insulators were: 1) a cloth "split sheet" surgical drape (Superior Surgical, Seminole, FL); 2) a paper split sheet (Baxter Healthcare Corp., Deerfield, IL); 3) a Thermadrape™ disposable metallic paper laparotomy sheet (O.R. Concepts, Inc., Roanoke, TX); 4) an unheated Bair Hugger® patient-warming blanket (Augustine Medical, Inc., Eden Prairie, Minnesota); 5) a prewarmed cotton hospital blanket; and 6) plastic garbage bags. Each insulator provided complete single-layer coverage below the neck. Thermal flux transducers measured cutaneous heat loss at 10 area-weighted sites.

Cutaneous heat losses decreased significantly from ≈100 W during control to ≈65 W when volunteers were covered. We found no clinically important differences in heat loss between the coverings. Furthermore, a pre-warmed cotton cover transferred little heat to volunteers.

These data indicate that a thin layer of the tested materials provides substantial thermal protection. However, the benefits of each material are similar, suggesting that covered surface area is more important than the nature of the covering. Thus, choice of perioperative covers should depend on other factors such as cost, convenience, sterility, and patient comfort.

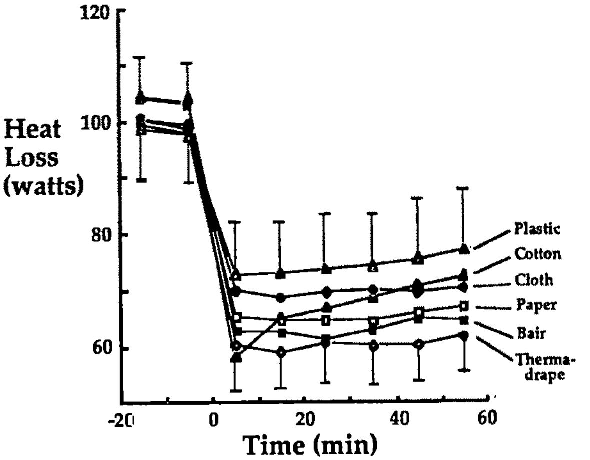


Figure: Mean cutaneous heat loss (± SD) in volunteers covered with a variety of insulating materials. There was no clinically important difference between the insulators.

Supported by National Institutes of Health grant #R29 GM39723.

S176

TITLE: CARDIOVASCULAR EFFECTS OF HALOTHANE IN YOUNG AND ELDERLY ADULTS

AUTHORS: M.S. McKINNEY MB. & J.P.H. FEE MD.
AFFILIATION: DEPARTMENT of ANAESTHETICS, THE QUEEN'S UNIVERSITY of BELFAST, NORTHERN IRELAND

INTRODUCTION: Although halothane is known to reduce cardiac output, it may be favoured over isoflurane because of the risk of coronary steal. There is little documentation of the cardiac effects of halothane in the elderly and this study examines these in both young and elderly adults when given in a dose of 1 MAC.

METHOD: 40 consenting patients matched for height, weight and gender, aged 18 to 40 years (n=20) and over 60 years (n=20) were included in the investigation approved by the University Research Ethical Committee. All patients were healthy (ASA 1 or 2) and not taking any cardio-active medication.

ECG was continuously displayed and blood pressure recorded every minute with an automatic oscillo-tonometer. Cardiac output measurements were made by one operator with a Datascope Accucom using the supra-sternal approach. Volatile agent concentration was measured using a Datex Normac and the end tidal value along with blood pressure, heart rate and cardiac output was recorded on line by a micro-computer. Cardiac output was converted to cardiac index for analysis. After baseline recordings, etomidate 0.3 $mg.kg^{-1}$ was used for intravenous induction, with atracurium 0.5 $mg.kg^{-1}$ to allow intubation with a gas monitoring tracheal tube. IPPV was commenced with 100% oxygen and, 2 minutes after intubation, halothane was added to rapidly achieve and maintain 1 MAC (corrected for age) end-tidal concentration. Measurements were repeated every 2 minutes for a 20 minute period prior to surgery.

RESULTS: The data were analysed statistically using repeated measures analysis of variance and $p<0.05$ was considered significant. The mean ages±SD in the 2 groups were 72.1±5.84 and 29.4±5.37 years.

Both groups showed similar reductions in heart rate and diastolic blood pressure, but the elderly had a significantly greater reduction in systolic and mean blood pressures. Cardiac index showed a similar fall from baseline in the two groups.(Table 1).

DISCUSSION: Halothane causes a significantly greater fall in blood pressure in the elderly but the reduction in heart rate and cardiac index is similar in both age groups.

	Young		Elderly	
	Baseline	20 mins	Baseline	20 mins
HR	74.4±10.08	66.3±13.25	74.1±11.05	63.6± 7.60
SBP	126.5±14.61	105.4±11.31	145.0±23.87	115.6±17.71
DBP	68.2± 8.56	54.9± 8.20	111.7±17.27	87.6±12.10
MAP	92.8±11.98	82.3±10.67	85.1±17.04	69.2±13.23
CI	3.7± 0.98	2.9± 0.55	3.2±1.15	2.7± 0.63

Table 1. Baseline and 20 minute means±SD for the cardiovascular parameters in both young and elderly.

S177

TITLE: CARDIOVASCULAR EFFECTS OF ISOFLURANE IN YOUNG AND ELDERLY ADULTS

AUTHORS: M.S. McKINNEY MB. & J.P.H. FEE MD.
AFFILIATION: DEPARTMENT of ANAESTHETICS, THE QUEEN'S UNIVERSITY of BELFAST, NORTHERN IRELAND

INTRODUCTION: Isoflurane has a deserved reputation for safety, with many studies demonstrating its lack of depression of cardiac output. Although these studies have mostly been performed on young adults, the results are also applied by most clinicians to the elderly. This study examines the cardiovascular effects of 1 MAC isoflurane on both populations.

METHOD: 40 consenting patients matched for height, weight and gender, aged 18 to 40 years (n=20) and over 60 years (n=20) were included in the investigation approved by the University Research Ethical Committee. All patients were healthy (ASA 1 or 2) and not taking any cardio-active medication.

ECG was continuously displayed and blood pressure recorded every minute with an automatic oscillotonometer. Cardiac output measurements were made by one operator with a Datascope Accucom using the supra-sternal approach. Volatile agent concentration was measured using a Datex Normac and the end-tidal value along with blood pressure, heart rate and cardiac output was collected on line by a microcomputer. Cardiac output was converted to cardiac index for analysis. After baseline recordings, etomidate 0.3 $mg.kg^{-1}$ was used for induction with atracurium 0.5 $mg.kg^{-1}$ to allow intubation with a gas monitoring tracheal tube. IPPV was commenced with 100% oxygen and, 2 minutes after intubation, isoflurane was added to rapidly achieve and maintain 1 MAC (corrected for age) end tidal concentration. Measurements were repeated every 2 minutes for a 20 minute period prior to surgery.

RESULTS: The data were analysed statistically using repeated measures analysis of variance and $p<0.05$ was considered significant. The mean ages±SD in the 2 groups were 69.8±7.10 and 28.7±6.63 years.

Both groups showed similar reductions in systolic, diastolic and mean blood pressures. The young adults showed a moderately increased heart rate throughout the study while the elderly heart rates returned to baseline. There was a significant difference in change in cardiac index between the groups with a fall in the means from 3.36 $l.min^{-1}.m^{-2}$ to 2.55 $l.min^{-1}.m^{-2}$ in the elderly and from 3.575 $l.min^{-1}.m^{-2}$ to 3.515 $l.min^{-1}.m^{-2}$ in the young. (Fig. 1).

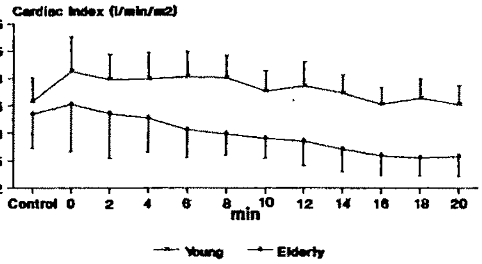


Fig. 1.
Cardiac Index with 1 MAC Isoflurane
95% Confidence Intervals

S178

TITLE: INHALATIONAL INDUCTION WITH ISOFLURANE IN ADULTS

AUTHORS: M.S. McKINNEY, MB. & J.P.H. FEE. MD.
AFFILIATION: DEPARTMENT OF ANAESTHETICS, THE QUEEN'S UNIVERSITY OF BELFAST, NORTHERN IRELAND

INTRODUCTION: Inhalational induction is not commonly used in adults but does offer advantages: cardiovascular stability, safe maintenance of airway patency and negligible after effects of anesthesia.

METHOD: Sixty healthy patients (ASA 1 or 2) aged 18 to 65 were studied after approval by the University Ethical Committee and their informed consent.

Monitoring of blood pressure and ECG were commenced prior to induction. A standard anesthetic gas mixture of 37% oxygen in nitrous oxide was delivered via a Bain circuit at a fixed minute volume of 8 l. Patients were randomly allocated to one of four groups (n=15) to receive either isoflurane or halothane with or without CO_2 (0.4 $l.min^{-1}$ for 90 seconds). The vaporizer setting was increased by 0.5% every 10 seconds to a maximum of 5%. Coughing and excitation (breath holding or involuntary activity) were separately graded and scored as 0 (None), 1 (Mild) and 2 (Severe). The assessor was unaware of the patient's group.

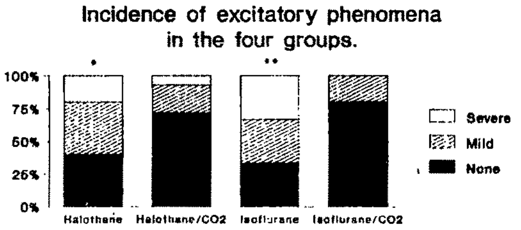
RESULTS: Results were interpreted using analysis of variance, Kruskall Wallis and the Mann Whitney-U test, with $p<0.05$ indicating significance. The groups were similar with regard to weight, sex and the incidence of smoking or pre-medication. The acceptance of the technique was very high, and showed no relationship with the volatile agent or to CO_2. Recall of induction was limited to the first few breaths from the mask.

Isoflurane induction abolished the eyelash reflex significantly earlier than halothane (mean difference 16.5 secs), but the presence of CO_2 had no effect.

Isoflurane produced a significantly higher incidence of cough, but there was no difference between the agents for excitatory phenomena. The addition of CO_2 resulted in a significant reduction in excitation with both agents - isoflurane with CO_2 producing significantly less excitation than halothane alone. (Fig. 1)

$PaCO_2$ did not appear to be changed in the CO_2 groups.

DISCUSSION: The addition of 5% carbon dioxide to isoflurane/nitrous oxide anesthesia facilitates inhalation induction in adults.



(* p<0.05 compared with Isoflurane/CO2)
(** p<0.01 compared with Isoflurane/CO2)
Figure 1.

S179

Title: Desflurane: How Does It Compare to Isoflurane in Elderly Patients?

Authors: Donald W. McMillan, II, M.D., Martin I. Gold, M.D., Everard A. deLisser, M.D., Nick N. Palermo, M.D

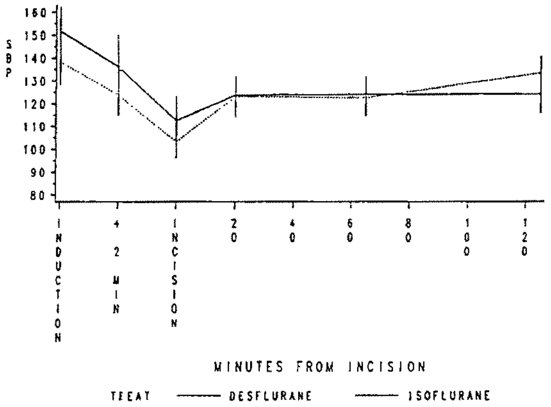
Affiliation: VA Medical Ctr. and Univ. of Miami School of Med., Dept. of Anesthesiology, Miami, FL

Introduction: The purpose of this investigation was to compare hemodynamic, laboratory, recovery and safety characteristics of Desflurane (DES) vs. Isoflurane (ISO) in elderly patients.

Methods: After obtaining permission from the Internal Review Board and from each patient, 43 patients age > 65, ASA I-III, scheduled for orthopedic, plastic, ENT or general surgery, were randomly assigned to: DES, n=22, or ISO, n=21. All unpremedicated patients received 3 mg curare and 1 mcg/kg fentanyl (FENT) 3 min prior to induction and intubation with 3-5 mg/kg of thiopental and 1.5 mg/kg succinylcholine. Anesthesia was maintained with 60% N_2O-O_2 and DES 3.0% or ISO 0.5% adjusted up or down. Vecuronium was used if needed, but no CNS depressants except FENT for hypertension and tachycardia. Hematology, urinalysis, electrolytes, liver enzymes and EKG were obtained pre- and post-operatively. Standard sensors and monitors were used plus a DATEX Capnomac or SARA calibrated for DES and ISO respectively. Recovery times and hemodynamics in the PAR were assessed.

Results: There was no difference in ASA ratings, age (mean – 70 years), weight, or height in either group. Mean % peak end-tidal agent was DES 8.5 ± 0.7 and ISO 1.7 ± 0.2. At surgery's end the % mean end-tidal was: DES 2.6 ± 0.4 and ISO 0.5 ± 0.1. Duration of anesthesia was: DES 177 vs. ISO 161 min. There was one FENT administration with 1 DES patient and 15 treatments in 8 ISO patients ($p < 0.05$). There was no statistically significant difference in any emergence or hemodynamic parameters intra-operatively (figure).

Conclusion: No difference was seen between DES and ISO concerning hemodynamics, wake up time, complications, laboratory or EKG values. The significant difference was FENT administration for hypertension and tachycardia: ISO-8; DES-1. We conclude that DES in elderly patients is as efficacious and safe as ISO.



S180

Title: HYDROXYPROPYL-B-CYCLODEXTRIN CAN POTENTIATE THE ANALGESIC PROPERTIES OF SPINAL SUFENTANIL IN RATS

Authors: T. Meert PhD, J. Mesens PhD, P. Verheyen IR, H. Noorduin, M. Vercauteren MD.

Affiliation: Department of Neuropsychopharmacology, Janssen Research Foundation, B-2340 Beerse, Belgium

Introduction: The lipophilicity of spinally applied opioids can codetermine the onset and duration of analgesia as well as the appearance of an early or late respiratory depression. One way to modulate the lipophilicity of opioids, without changing the properties of the free drug itself, is molecular sequestration using hydroxypropyl-B-cyclodextrin (HP-B-CD). A systematic behavioural study on the spinal activity of various doses of sufentanil in different concentrations of HP-B-CD was performed.

Methods: The study was approved by the Institutional Committee for Animal Research. Male Wistar rats were equiped with an epidural or intrathecal catheter under general anesthesia and 4 days later tested. In a first experiment, the activity of 1 µg sufentanil in various concentrations of HP-B-CD was tested. In a second experiment, dose response functions of sufentanil in 0 and 10 % HP-B-CD were established. For both experiments, tail withdrawal reaction time (TWR > 6.0 and ≥ 10.0 sec), blockade of pinna and cornea reflexes and muscle tone were scored repeatedly over time after spinal treatment. Finally, the effects of a fixed dose of sufentanil (2 x ED_{50} for a TWR ≥ 10.0 sec) in 0 and 10 % HP-B-CD were evaluated on arterial PO_2 and PCO_2 levels. All spinal injections were given in 20 µl.

Results: Increasing the concentration of HP-B-CD from 0 to 10 % resulted in a 1.3 to 1.9 and a 2.0 to 2.9 fold increase in the duration of analgesia obtained with 1 µg sufentanil after epidural and intrathecal treatment, respectively. Higher concentrations of HP-B-CD were less effective. The results of the dose response functions of sufentanil in 0 and 10 % HP-B-CD are given in table 1. Twice the ED_{50} of sufentanil for a TWR ≥ 10 sec in 0 % HP-B-CD clearly reduced PO_2 and increased PCO_2 levels between 5 and 90 min after both epidural and intrathecal treatment. Comparable doses of sufentanil in 10 % HP-B-CD were without any effect on respiration up to 8 h after injection.

Discussion: HP-B-CD can potentiate the activity of sufentanil after epidural and intrathecal treatment in rats. This potentiation was present in terms of a longer duration of analgesia after a fixed dose of sufentanil, and in a reduction of the lowest ED_{50}s to produce analgesia. The potentiation of analgesia was accompanied by an increase in specificity and a lack of any effect on respiration. Maximal activity was measured after inclusion complexation of sufentanil in 10 % cyclodextrin. At higher concentrations of HP-B-CD, both the activity and the specificity appeared to reduce. These results can be described in terms of a longer availability of sufentanil at the spinal level after injection in cyclodextrin. As a result, there is less sufentanil available for redistribution in lipid tissue and in the circulatory system, producing less systemic side-effects.

Table 1: Epidural and intrathecal ED_{50}s of sufentanil

Raw	Index	0 % HP-B-CD		10 % HP-B-CD	
		epi	intra	epi	intra
A	TWR > 6.0 sec (µg)	0.26	0.26	0.025	0.032
B	TWR ≥ 10.0 sec (µg)	0.58	0.29	0.079	0.032
C	Pinna reflex (µg)	1.02	0.77	0.85	0.31
D	Ratio C/A	3.92	2.96	34.0	9.69
	C/B	1.75	2.66	10.76	9.69

S181

Title: COMBINED EFFECTS OF VERAPAMIL AND HALOTHANE ON PRESSURE RECOVERY AFTER HYPOPERFUSION IN GUINEA PIG HEARTS

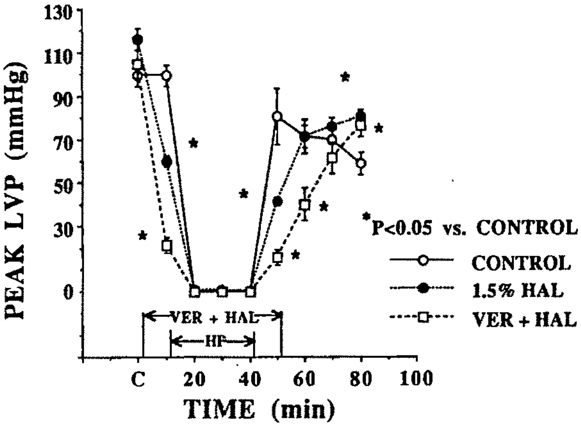
Authors: RW Mehner, N Buljubasic MD, M Boban, MD, DF Stowe MD PhD, JP Kampine MD PhD, and ZJ Bosnjak PhD

Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

Temporary global ischemia resulting from tissue hypoperfusion (HP) can cause significant impairment of cardiac function.[1] The purpose of this study was to examine the protective effects of verapamil (VER) and halothane (HAL) combined vs. HAL alone on functional recovery of LVP and the duration of ventricular fibrillation (VF) following global ischemia.

After institutional approval, 30 guinea pig hearts were isolated and perfused by the Langendorff technique at control perfusion pressure (PP) of 55 torr with modified Krebs solution at 36.5°C. Bipolar recording electrodes were placed in the right atrium and ventricle to monitor rhythm and a balloon was placed in the left ventricle to measure left ventricular pressure (LVP). Hearts were divided into 4 groups and each group was exposed to HP at 0% PP: control n=10; VER n=6; HAL n=8; HAL+VER n=6. Drugs were given 10 min prior to, during, and 10 min following HP. HAL concentration in the perfusate was 295±15 µM. The duration of HP was 30 min; this was followed by 40 min of reperfusion at control PP. Statistical differences were analyzed by ANOVA (means±SEM).

Although the addition of VER+HAL significantly decreased LVP to 20% of control prior to and 15% of control 10 min after HP, there was no significant difference from the LVP recovery of the HAL group after 40 min of reperfusion (figure).



Both HAL+VER and HAL groups had a significantly higher recovery than the control group after 40 min of reperfusion while the VER group did not significantly improve. The duration of VF was reduced in the treatment groups vs. the control group although there was no difference between the treatment groups. The combination of VER+HAL 10 min prior to HP dramatically decreased the contractile force in comparison with the control and HAL groups alone. Although the cardiac work was suppressed further in the VER+HAL group, this did not contribute to the final recovery of peak LVP following 40 min reperfusion.

Our results indicate that HAL has protective effect on LVP and VF. No further improvement was seen with the addition of VER. **Reference:** 1) *FASEB J* 3:A848,1989.

S182

TITLE: ASSESSMENT OF VITAL CAPACITY BREATHING DURING DENITROGENATION

AUTHORS: M.P. Mehta, M.D., J.S.T. Sum-Ping, M.D., T. Symreng, M.D., Ph.D.

AFFILIATION: Department of Anesthesia, University of Iowa, Iowa City, IA 52242

Vital capacity breathing during denitrogenation has been suggested as an alternative to normal pattern of breathing prior to "rapid-sequence" induction of anesthesia[1]. The goal of denitrogenation is to provide an adequate oxygen reserve in patients to avoid hypoxia during the period of apnea. The aim of this study was to compare and assess adequacy of oxygen reserve and rate of denitrogenation during normal and vital capacity breathing.

Method Seven volunteers, ASA I, were studied with informed consent and approval from University Human Research Review Committee. Each volunteer, with nose clipped was required to breath through a mouth piece connected to the circle system on three separate sessions - A, B and C. Breathing patterns for different sessions were as follows: A - Normal breathing, B - four vital capacity breaths followed by normal breathing and C - continuous vital capacity breathing. In all three sessions, a 10 L/min oxygen flow rate was delivered to the circle system primed with oxygen. Inspired and expired gas analysis (Ohmeda gas analyzer 6000) were done and time to 5% nitrogen in expired gas was recorded. Statistical analysis was performed using paired t-test, $P<0.05$ was considered statistically significant. Results are expressed as mean ± S.D.

Results

The time to 5% nitrogen in expired gas were 126 ± 31, 97 ± 28 and 94 ± 12 secs. during session A, B, and C, respectively. The time obtained during session A was longer than that in session B ($P=0.05$) and session C ($P<0.05$). Expired nitrogen level at end of fourth vital capacity breath (session B) was 14 ± 4.0%.

Discussion

Denitrogenation to 5% can be achieved in about two minutes with normal breathing pattern. Though the same degree of denitrogenation was not reached with four vital capacity breaths the time for nitrogen level to come down to 5% can be shortened by breathing continuously at vital capacity.

Reference

1. Gold MI, et al: Anesth Analg, 1981; 60:313-315.

S183

Title: **Improving Preoperative Laboratory Test Selection**

Authors: P Meyer, MS, R Thisted, PhD, MF Roizen, MD, G Gronert, MD, WJ Murray, MD, PhD, AW Grogono, MD, P Duke, MD, S Kim, AB, J Apfelbaum, MD, G Rupani, MD, P Texidor, PhD, PF White, MD, PhD, SM Poler, MD, D Coalson, MD, JA Youngberg, MD, R Dionne, DDS, C Stocking, PhD

Affiliation: Depts of Anesthesia and Critical Care and Statistics, University of Chicago, Depts of Anesthesia at Univ of Cal Davis, Duke Univ, Washington Univ at St. Louis, Tulane, Univ of Manitoba, and Archbishop Bergan Hospital

Introduction: Selection of preoperative laboratory tests has largely been based on "expert" opinion. After a risk benefit analysis, derived from the frequency of abnormal results obtained for a particular test in a general population, the expert recommends test selection. For example, an FDA panel on presurgical radiography concluded that a chest x-ray (CXR) need not be obtained in asymptomatic individuals < 60 years of age; for individuals > 60 years old, the data were inconclusive. But the data the panel examined did not include patient history. We sought to determine whether a patient's history could be used to improve test selection preoperatively.

Methods: With the approval of the review board of each institution and with patient consent, 1300 patients completed an automated, standardized, computer-stored health history questionnaire, HealthQuiz. We reviewed the results, including patient age and changes in care (as indicated by the patient's anesthesiologist or surgeon) to determine whether age or elements of patient history could predict significant test abnormalities that might warrant treatment or changes in care.

The method of analysis we chose was recursive partitioning. With this method, a sample population is divided into subsamples on the basis of the answer to a single question. If we are trying to predict the need for a preoperative CXR for patients > 59 years of age for instance, it may be that a CXR is warranted 85% of the time for certain patients (cigarette smokers) and only 20% of the time for others. Recursive partitioning enables us to select the most relevant information from that obtained by a patient history. Thus, smoking history splits our sample before age or other variables. We then focus on nonsmokers (of whom only 20% require CXR) and divide this group again, perhaps by age, if doing so increases our ability to predict the need for CXR. In a similar fashion the group of smokers (85% of whom should have a CXR) can be partitioned again by other relevant items of patient history. The result of an analysis of this sort is a decision tree, often based on a small number of questions that optimally predicts the need for a particular diagnostic test.

Results: We can refine preoperative test selection using recursive partitioning. For example, recursive partitioning indicates groups of asymptomatic individuals who do not benefit from CXR until after their 74th birthdays (some asymptomatic individuals < 74 years old will benefit, but more will be harmed—thus the use of groups).

Conclusion: We conclude that using information from patient history can improve laboratory test selection and reduce cost and the possibility of harm to preoperative patients.

Reference: JAMA 253:3576-3581, 1985.

S184

Title: POSTTHORACOTOMY PAIN: CRYOANALGESIA VERSUS INTRAPLEURAL ANALGESIA

Authors: R. Miguel, M.D., D. Hubbell, M.D.

Affiliation: Departments of Anesthesiology and Surgery, University of South Florida College of Medicine, Tampa, Florida 33612-4799

Introduction: Management of postoperative thoracotomy pain varies widely and includes cryoanalgesia, intrapleural analgesia, and parenteral analgesia. We wished to evaluate the relative efficacy of these methods for the control of postthoracotomy pain.

Methods: After IRB approval, consenting ASA class II and III patients who were 44 to 74 years old and were undergoing antero- or posterolateral thoracotomy were randomly assigned to one of three groups. Cryoanalgesia (CA) was given to nine patients with a 30-second freeze of the intercostal nerve trunks at the costovertebral angle. Intercostal nerves at the level of incision, one above, and one below were frozen. Five patients received intrapleural analgesia (IP) with a catheter inserted percutaneously at the operative level and threaded under direct vision 5 cm cephalad. Twenty ml of a 0.5% bupivacaine with 1:200,000 epinephrine was administered every six hours. Seven patients were given intravenous morphine (PA), 2 to 4 mg, on request. If patients in any group complained of pain, an intravenous infusion of 2 to 4 mg of morphine sulphate was administered until acceptable pain relief was achieved. The intensity of pain was recorded on the day of the operation, and on postoperative days one, two, and five, using a 0 to 100 mm visual analog scale (VAS). Data are summarized as mean ± SD. The amount of morphine given daily was statistically evaluated with an analysis of variance. Visual analog scale scores were statistically evaluated with the Kruskal-Wallis test.

Results: No significant differences in the intensity of pain were noted among patients who received cryoanalgesia, intrapleural analgesia, or parenteral analgesia at any time (Table 1). In addition, despite a wide range of morphine dosage in each group, no differences were noted among the groups in the amount of morphine administered (Table 2).

Table 1: Visual analog scores (mm).

	Day 0	Day 1	Day 2	Day 5
CA	48±24	29±18	20±22	26±22
IP	47±32	39±26	27±11	37±15
PA	62±31	44±26	26±14	24±18
p=	0.49	0.41	0.24	0.12

Table 2: Daily morphine dosage (mg).

	Day 0	Day 1	Day 2	Day 5
CA	19±9	25±9	17±10	5±6
IP	20±14	24±12	18±19	5±4
PA	18±11	31±16	33±14	7±10
p=	0.92	0.40	0.10	0.88

Discussion: In addition to the obvious discomfort, postthoracotomy pain may cause significant morbidity. Numerous forms of therapy have been suggested.[1,2] We found that intravenous morphine, cryoanalgesia, and intrapleural analgesia provided equivalent pain relief.

Reference:
1. Thorax 35:325-327, 1980
2. Can J Anaesth 36:106-109, 1989

S185

TITLE: THE EFFECT OF POSITIONING AND OBESITY ON EPIDURAL ANALGESIC SPREAD

AUTHORS; Milligan KR, MD; Cramp P, FCAnes; Schatz L, MD; Johnston D, MD; Carp H. MD.

AFFILIATION: Department of Anesthesia, Oregon Health Sciences University, Portland, Oregon.

INTRODUCTION: Epidural analgesia is a common method of providing pain relief during labour but factors affecting the spread of solutions have not been adequately defined. Most authorities recommend reduced dosages in the obese (1,2) but Hodgkinson and Husain (3,4) found a decreased spread in obese cesarean section patients when the injection was made in the sitting position. In contrast the lateral position produced increased spread. These studies included few obese patients and relied on retrospective controls. A later study by Park et al (5) concluded that position has no effect on epidural spread. The purpose of this study is to assess the effect of position on the spread of epidural analgesia in obese patients requiring pain relief in labor and to compare them with a normal control group.

METHODS: Eighty healthy parturients with singleton cephalic presentations requesting epidural analgesia in labor were recruited into the study. Forty patients weighing <80 kg were allocated to a control group (A) and a further 40 weighing >100 kg were allocated to a study group (B). Following informed consent 20 patients in each group were randomly allocated to receive their epidural in the sitting position, the remaining 20 receiving theirs in the lateral position. All patients received routine monitoring and intravenous fluid therapy. Following skin preparation the epidural catheter was inserted at the L3-4 interspace and threaded 3 cm cephalad. A test dose of 3 ml 0.25% bupivacaine plain was injected followed by a further 9 ml 2 minutes later. The patients remained either sitting or lying for a further 5 min before moving to either the left or right lateral positions. The extent of the block was assessed using loss of cold sensation at 10 minute intervals for 40 minutes.

RESULTS: Data analysis using the Mann-Whitney U test demonstrated no intragroup demographic differences (Table 1). The group B (obese) patients were taller (p<0.005), than the group A patients but their body mass index (BMI), a measure of obesity, was still significantly greater (p<0.005). With respect to block height there were no differences between groups A and B and patient position had no effect. At 40 min block height was T8/T8 (mean/median) for all 4 groups

DISCUSSION: Previous studies on epidural spread, using larger doses of solution, have investigated patients undergoing surgical procedures. The results of the present study indicate that for routine labor epidurals using 12 ml of 0.25% bupivacaine plain neither patient obesity nor positioning affect the height of the block obtained.

Table 1. Summary of demographic data (Mean±SD)

Group	Age (yr)	Weight(kg)	Height (m)	BMI
A lat	24.3±6.6	68.8±6.2	1.59±0.065	27.1±3.17
A sit	22.3±5.7	67.2±7.8	1.61±0.070	25.8±2.83
B lat	25.4±5.4	114.5±14.4	1.69±0.066*	40.2±4.31*
B sit	24.3±4.6	114.3±13.2	1.59±0.074*	39.8±4.49*

*difference from A (p<0.005)

REFERENCES:

1. Warner WA, Garrett LP. JAMA 205: 92-93, 1968.
2. Buckley FP et al. Anaesthesia 38: 40-51, 1983.
3. Hodgkinson R,Husain FJ.Anesth Analg 59:89-92,1980.
4. Hodgkinson R,Husain FJ.Anesth Analg 60:421-4,1981.
5. Park WY et al. Anesth Analg 64:863-864, 1984.

S186

LIDOCAIN -HCl OR -CO_2 FOR BRACHIAL PLEXUS BLOCK IN PATIENTS WITH CHRONIC RENAL FAILURE ?

G. Mitterschiffthaler,
Department of Anaesthesia and General Intensive Care, University of Innsbruck, Austria.

Introduction: Brachial plexus blockades have been reported to have a 38% shorter duration of action in patients with renal failure.[1]

This prospective study compares the latency and duration of analgesia after axillary block with lidocain -HCl and -CO_2 between patients with and without chronic renal failure.

Material and Methods: An uniform axillary blockade technique was used without a nerve stimulator. 24 uraemic patients required nerve block for a/v fistulas on the forearm, the other 24 healthy patients were scheduled for orthopedic surgery of the hand. The total volume of local anaesthetic injected was 25ml/m^2 of body surface. The local anaesthetics used were plain 1% lidocaine -Cl and -CO_2. Latency of analgesia was determined by dullness to the pinprick method of the surgical site. Onset of analgesia of the dermatomas of the Nn. radialis, ulnaris and musculocutaneus was also determined. Duration of analgesia was defined as time difference between complete analgesia and first pain at the operation site.

Results: Biometric Data (mean +SD)

	RENAL	FAILURE	CONTROL	GROUP
	L - Cl	*L- CO_2*	*L-Cl*	*L-CO_2*
n	12	12	12	12
Age (yr)	45+15	49+12	39 +16	43 +14
Sex (F/M)	10/2	8/4	9/3	8/4
Creatinine	10,4 + 3,6	9,6 + 3,1	0,8 + 0,2*	0,9 + 0,2*
Hb	7,6 + 1,2	7,4 + 0,9	14,2+0,4*	14,3 + 0,3*
Volof LA	42 + 3	44 + 4	41 + 5	39 + 6
Latency op. site(min)	8,5 + 1,8	7,2 +0,9	7,9 + 2,1	7,1 +1,9
Duration of block (min)	256 + 35	231 + 32	269 + 41	244 + 43

(*t-test<0,5), L-Cl:lidocainhydrochlorid, L-CO_2:carbonated lidocain

Discussion:
There are some differences between the studies of Bromage and Martin[1,2]: Bromage used a constant volume, the supraclavicular approach and several types of local anaesthetic agents, whereas Martin used higher volumes and lidocain plus epinephrin. We reduced the volume slightly because of the risk of toxicity according to the body surface. The shorter duration of the block could be due to a higher cardiac index, because these patients adapt to anaemia and cardiac insufficiency quite well. On the other hand uraemic neuropathy may lead to a slowing of conduction in proximal nerve trunks and plexus that would lead to a relative sensitivity for local anaesthetics and prolonged duration of the block. In clinical routine we could not find any difference in onset time between normal lidocain and the carbonated agent in acidotic patients.

Conclusion: Latency and duration of analgesia are not significantly different between patients with and without chronic renal failure. Also in this high risk group both local anaesthetic agents could be used in higher doses without side effects.

References

1.) Bromage PR,Gertel M. Anesthesiology: 1972, 36:488 - 493
2.) Martin R Beauregard L, Tetrault PP. Anaesthesiology: 1988, 69:405 - 406

S187

Title: EEG-QUANTIFIED ANESTHESIA: INFLUENCE ON MYOCARDIAL INFARCTION RATE DURING CAROTID ENDARTERECTOMY

Authors: P.A. Modica, M.D., W.S. Jellish, Ph.D., M.D., R. Tempelhoff, M.D.
Affiliation: Dept of Anesthesiology
Washington University
St. Louis, MO 63110

To prevent cerebral ischemia during carotid cross-clamping, many advocate the use of alpha-pressors to raise the mean arterial blood pressure (MAP). Unfortunately, it appears that this treatment increases the risk of myocardial ischemia during carotid endarterectomy (CEA) (1). In the following study we employed an EEG quantified depth of anesthesia in an effort to decrease the use of alpha-pressors during CEA.

Following institutional approval, 170 consenting patients undergoing CEA were studied. After slow induction with thiopental (2-4 mg/kg) or etomidate (0.3-1.6 mg/kg), general anesthesia was maintained with 70% N_2O in O_2, isoflurane (0.1-0.25% ET) and a fentanyl infusion. A 2 channel computerized EEG (CEEG) was used to monitor anesthetic depth and detect signs of cerebral ischemia (2). MAP was maintained within ±15% of baseline. Hypertension was treated with isoflurane (0.1-0.25% ET) and/or vasodilators. Hypotension, without CEEG ischemic signs, was treated with fluid infusion and decreases in isoflurane. CEEG frequency was maintained below 12-15 Hz, mostly delta, theta and low alpha. Alpha-pressors were employed during clamping only if EEG-based selective shunt placement did not correct the EEG signs of ischemia.

Eight patients required alpha-pressor support (5%). In 2 of these 8 patients the CEEG signs of ischemia appeared during closure when shunting was no longer possible. In 1 of these 2 patients the increase in MAP did not improve his CEEG tracing, and he suffered a CVA (0.6%). Two patients (1.2%) suffered a nonfatal MI (CPK MB +) without major clinical consequences. No other patients suffered a CVA or MI. One patient had an episode of awareness diagnosed by the appearance of beta activity on CEEG and required a repeat dose of etomidate.

Previous studies have demonstrated that routine MAP support during CEA with alpha-pressors increases the risk of MI 3-4 fold when compared to anesthesia without such pharmacological intervention (1,3). Our results under general anesthesia show a low incidence of CVA and MI (with 0% fatal MIs) similar to other large series of CEAs performed using local anesthesia (4). The maintenance of MAP and cerebral perfusion pressure during CEA can be accomplished with the use of EEG quantified anesthesia without pharmacological MAP support, thus decreasing the risk of perioperative MI.

(1) Anesthesiology 69:846, 1988
(2) Neurosurgery 24:339, 1989
(3) Surgery 85:249, 1979
(4) Can Anaesth Soc J 31:192, 1984

S188

TITLE: PROPOFOL INFUSION: SEDATIVE, AMNESTIC, AND ANXIOLYTIC EFFECTS

AUTHORS: T.G. Monk, M.D., I. Smith, M.D., P.F. White, Ph.D., M.D.
AFFILIATION: Department of Anesthesiology, Washington University, St. Louis, MO 63110

Propofol is a rapid and short-acting intravenous (iv) anesthetic which has been used for sedation during regional anesthesia. We designed a randomized, double-blind study to assess the sedative, amnestic, and anxiolytic effects of propofol when infused at a constant rate during spinal anesthesia.

40 unpremedicated, consenting male adults, ages 52-90 yr, undergoing elective urologic procedures were randomly assigned to one of four sedation treatment groups according to an IRB-approved protocol. After achieving adequate spinal analgesia (T_{9-10} level), patients were administered one of four infusion regimens using a Baxter pump. A loading dose of propofol 0.2, 0.4, 0.5, or 0.7 mg/kg was infused over 2-3 min, followed by a constant infusion of 0.5, 1, 2, or 4 mg/kg/h, respectively. Blood pressure, heart rate, respiratory rate and SaO_2 were recorded at 5 min. intervals. The patients and the anesthesiologist evaluated sedation and anxiety levels (0 = none to 100 = maximal) at 0, 15, 30, 45, and 60 min. after initiating the loading dose. In addition, pictures were shown to the patients at times 0, 30, and 60 min. At the time of discharge from the PACU, intraoperative recall and patient satisfaction was assessed using a questionnaire. Data were analyzed using repeated measures of ANOVA and Chi-square tests, with $p<0.05$ considered significant (mean values ± S.D.).

The four treatment groups were comparable demographically. Propofol, 0.5 to 4 mg/kg/h, produced dose-dependent sedation (table 1). Anxiety levels were non-significantly decreased (fig. 1). Intraoperative amnesia was only present at infusion rates of 2 and 4 mg/kg/h (fig. 2). No significant changes in the cardiorespiratory variables were noted during the infusion period.

In conclusion, propofol infusion, 0.5-4 mg/kg/h, produced stable levels of sedation during spinal anesthesia without cardiorespiratory depression. Lack of recall was only observed in patients receiving the highest infusion rates, suggesting that subhypnotic levels of propofol do not produce reliable amnesia.

Dose (mg/kg/h)	Mean sedation scores (mm) @0min	@15min	@30min	@45min	PACU
0.5	2±3	15±15	21±31	6±7	17±25
1.0	2±2	35±20	38±29	16±23	17±37
2.0	9±17	42±40	42±38	48±38	21±29
4.0	8±11	60±40	79±29	75±36	27±37

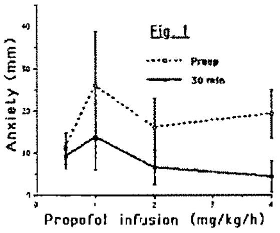


Fig. 1

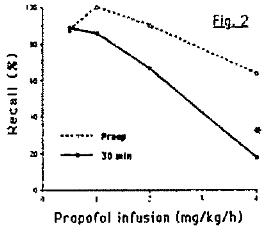


Fig. 2

S189

Title: COMPLICATION OF POSTOPERATIVE INTRAVENOUS AND EPIDURAL NARCOTIC ANALGESIA

Authors: CA Moote, MD WB Dobkowski MD, W E Komar RN.
Affiliation: Department of Anæsthesia, University Hospital, London, Ontario, Canada

Introduction: Anesthesiologists have pioneered the concept of the Acute Pain Service, offering more invasive pain management techniques to patients *outside* the operating room. The Acute Pain Service provides intravenous or epidural analgesia on general hospital wards. This is a very cost effective program because admission to the intensive care unit is avoided. The purpose of this study is to describe the complications associated with this program.

Methods: During the year 1989 we have prospectively collected utilization and complication data from our Acute Pain Service. Currently the most common types of analgesia are patient controlled analgesia (PCA) and continuous epidural analgesia (CEA). Patients for PCA are prescribed morphine 1-2 mg with lockout times of 6-10 minutes. Patients for CEA receive infusions of fentanyl 5–10 µg/ml, usually in combination bupivacaine with 0.5–1 mg/ml at a rate of 1 ml for each 10 kg body weight per hour. Patients are visited on daily rounds, when complications are recorded and analgesia is assessed using a visual analogue scale (VAS), from 0 mm = no pain to 100 mm = worst pain ever. Statistical comparison of the data was performed using unpaired t-tests and chi-square analysis at $p<0.05$.

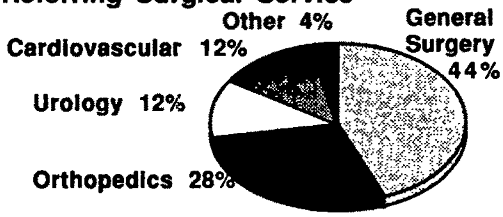
Results: The number of patients in the PCA and CEA groups were 274 and 182 respectively. Almost half the patients were from general surgery, the distribution of referring surgical services is shown in the figure. The CEA group experienced more complications (see Table). The VAS for the PCA and CEA groups were 35±2 and 26±3 (mean ± SEM) respectively.

Discussion: Our results indicate that PCA compared to CEA resulted in higher VAS pain scores but was associated with fewer complications. The difference in VAS was only 9 mm. Although this represents a statistically significant difference, it may not be a *clinically* significant difference. Therefore, PCA appears to be a somewhat less effective yet safer technique. Further study is needed to determine whether the benefits of CEA outweigh the risks.

Complications	PCA (% of	CEA patients)
Hypoventilation	0.4	2.6*
Hypotension	0.4	4.9*
Confusion	7.1	11.7*
Nausea	13.5	13.2
Pruritus	10.8	16.9*
Urinary Retention	0	4.5*
Motor Blockade	0	21*
Compliance	5	0*
Ineffective	2.4	6.8*
Technical	2.6	7.5*

* *different from PCA p<0.05*

Referring Surgical Service



S190

Title: SIMILAR INCIDENCE OF POST-DURAL PUNCTURE HEADACHE AFTER CONVENTIONAL VS CONTINUOUS SPINAL ANESTHESIA

Authors: CA Moote MD, GP Varkey MD, WE Komar RN.
Affiliation: Department of Anesthesia, University of Western Ontario, London, Ontario, Canada.

Introduction: The purpose of the study was to perform a prospective comparison of continuous spinal vs. conventional spinal anesthesia. The main objective was to determine the frequency of post-dural puncture headache in the two groups.

Methods: During a 15 month period from January '88 until March '89 we prospectively followed patients having conventional "single shot" spinal anesthesia and compared them to a similar group of patients having continuous spinal anesthesia, (with 20 gauge catheter). A registered nurse interviewed patients within 48 hours after surgery. They were questioned about postoperative complaints and if they did not voluntarily complain of headache they were specifically asked. Patients scored headache on a scale from 0–5; with 0 being no headache and 5 being the worst possible headache. The presence of post-dural puncture headache, headache scores, requirement for treatment and need for epidural blood patch were noted for each group. Statistical assessment was by unpaired student's t-test for parametric data and chi square for non paremetric data. A p value of <0.05 was considered statistically significant.

Results: We followed 289 patients. There was no detectable difference with respect to age and sex distribution between the two groups, as shown in the table. There were no complications related to infection or significant neurological deficit in either group. The incidence of headache in the conventional spinal group was 18/248 or 7%, and in the continuous spinal group 5/41 or 12%, this difference was not statistically significant. Epidural blood patch was performed in 2 patients, (both after a conventional spinal).

Discussion: Our results concur with others that the incidence of headache after continuous spinal anesthesia in geriatric inpatients is low[1,2] and is similar to conventional spinal anesthesia. Continuous spinal anesthesia, is a safe and effective technique which warrants further study.

Post-Dural Puncture Headache

	Conventional Spinal	Continuous Spinal
Patients (#)	248	41
Mean Age (yr)	69±10	70±10
Age Range (yr)	24–91	46–91
Sex (m/f)	188/60	25/16
No Headache		
Patients (#)	230	36
Mean Age (yr)	70±10	70±10
Headache no Treatment Required		
Patients (#)	11	0
Mean Age (yr)	69±15	0
Headache Score	2.5±0.8	0
Headache Treatment Required		
Patients (#)	7	5
Mean Age (yr)	59±13	71±7
Headache Score	4.3±1.3	2.8±1.9
Epidural Blood Patch		
Patients (#)	2	0
Total Patients with Headache		
Patients (#)	18	5

Values mean ± SD

References:

1. Int Anesthesiology Clin 27:46; 1989.
2. Regional Anesthesia 14 Number 2S:11, 1989.

S191

Title: DOES THE USE OF A SURGICAL TOURNIQUET INDUCE FEVER IN INFANTS?
Authors: LA Mostello, M.D., WF Casey, M.D. and WA McGill, M.D.
Affiliation: Children's National Medical Center, Washington, D.C.

Introduction. An increase in core temperature (CT) has been associated with use of surgical tourniquets in anesthetized pediatric patients.[1] Since the unconscious, paralyzed infant is usually at risk for intraoperative hypothermia,[2] we studied whether tourniquet-induced temperature (T) rise would still occur in a very young group of patients and manifest as fever (CT = 38.5°C).

Methods. The institutional review committee approved the protocol and waived the requirement for parental consent. We prospectively compared infants, 3 to 18 months of age, ASA physical status 1 and 2, free from infectious disease, undergoing procedures utilizing a unilateral tourniquet (TQ) to a similar group of patients undergoing hypospadius (H) repair. Surgery lasted 90 minutes or more. All were intubated and received oxygen, nitrous oxide and halothane with flow rates of 3L/min in a circle system, intravenous atropine (0.01-0.02 mg/kg), non-depolarizing muscle relaxants, and controlled ventilation to maintain end-tidal CO_2 at 30-35 mm Hg. Warming measures included a water mattress set at 37°C and a heat and moisture exchanger at the end of the endotracheal tube in all patients. No heating lamps were used. Esophageal T was recorded every 10 minutes from the time of surgical draping with three layers of cloth. If CT reached 38.5°C, cooling measures were instituted. Data were subjected to Fisher's exact test and ANOCOVA.

Results. In the TQ group 11/15 patients became febrile compared to 1/9 H patients ($p = .01$). Fever occurred 50 to 170 minutes after draping. Although both groups had a progressive rise in T, the overall slope of the TQ group was steeper ($p = .01$). In the TQ patients who became febrile, the average slope was 1.25°C/hr with a range of 0.80 to 1.61.

Discussion. In contrast to the expected hypothermia in infants,[3] all of our patients exhibited some rise in CT after draping for peripheral surgical procedures. The results confirm that infants may become febrile while undergoing procedures that utilize a limb tourniquet. Because orthopedic surgical procedures frequently require long operative times, fever may occur with the moderate rate of rise which we demonstrated.

References:

1. Ann Roy Coll Surg 68:193-4, 1986
2. Anaesth Int Care 13:300-4, 1985.
3. Anesth Analg 69:783-7, 1989.

S192

TRANSESOPHAGEAL ECHOCARDIOGRAPHY OF CONGENITAL HEART DEFECTS IN INFANTS AND CHILDREN

IA Muhiudeen, MD, DA Roberson, MD, NH Silverman, MD, MK Cahalan, MD, K Korver, MD, GS Haas, MD, K Turley, MD
University of California, San Francisco, California 94143

Introduction: To determine the role of intraoperative transesophageal echocardiography (TEE), prebypass and postbypass TEE were performed in 92 infants and children undergoing surgical correction of congenital heart defects.
Methods: The study protocol was approved by the Committee on Human Research at the University of California, San Francisco. The patients ranged from 4 days to 21 years (mean 4.1 years) and 3 to 68 kg (mean 15.4 kg). Sixty-eight patients had intracardiac shunt lesions, 30 had valvular regurgitation and 18 had obstructive lesions (some patients had both shunt and regurgitant lesions). TEE, including 2-D, color and pulsed Doppler, was performed with a 6.9 mm, 5 MHz, 26 element Aloka/Corometrics probe in 80/92 and with an adult sized probe in 12/92. Prebypass TEE was compared to the preoperative precordial echo, and direct visual intraoperative inspection and postbypass TEE was compared to postoperative precordial echo.
Results: High quality, two-dimensional images were obtained in 86/92 patients. The preoperative diagnosis was corrected in 3/92 and the preoperative diagnosis confirmed in 89/92. Two patients had an erroneous diagnosis of atrioventricular septal defect which was corrected by TEE. One patient had apical muscular VSDs which were not detected preoperatively by precordial echo but were correctly diagnosed with TEE. Postbypass TEE showed the absence of hemodynamically significant shunt lesions in all patients that had definitive shunt repairs (90%). TEE failed to adequately image supracristal VSDs in which the size of the defect could not be well delineated. Two patients had brief episodes of epistaxis during surgery which could have been attributed to TEE; otherwise, there were no complications from intraoperative TEE.
Conclusion: TEE provides accurate imaging of important morphologic features and flow characteristics in most pediatric congenital heart cases and provides an accurate assessment of the surgical repair.

S193

Title: Hemodynamic Responses and Recovery from Alfentanil in Children

Authors: John J. Mulroy, M.D., P.J. Davis, M.D., R. Cook, M.D.
Affiliation: Department of Anesthesiology, University of Pittsburgh, and Children's Hospital of Pittsburgh

Introduction: Alfentanil (Alf), a short-acting intravenous opioid, is a useful agent during short surgical procedures. This study compares intraoperative hemodynamic effects and recovery from combinations of alfentanil and halothane (halo).

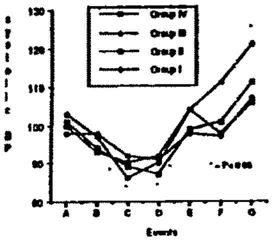
After institutional approval and informed consent, 80 unpremedicated ASA I-II patients, ages 2-12, undergoing elective surgery and endotracheal intubation were randomly assigned to 1 of 4 anesthetic regimens: I. Halo 0% ET/ALF 50 μg/kg; II. Halo 5%/alf 24 μg/kg; III. Halo 1.0%/alf 12.5 μg/kg; IV. Halo 1.5%/alf 0 μg/kg. General anesthesia was induced in all patients using a mixture of halothane and nitrous oxide. After attaining the proscribed ET halothane concentration, the calculated dose of alf was administered. Baseline heart rate (hr) and blood pressure (bp) were measured and recorded on admission to the hospital (A). They were recorded again at 1 minute before and after; alf administration (B, C); endotracheal intubation (D,E); surgical stimulation (F,G). Anesthetic maintenance consisted of nitrous oxide, the proscribed halo concentration and 12.5 μg/kg incremental doses of alf for increases of hr or bp. The times to extubation and alertness at completion of surgery were also recorded. Incidence of post-operative vomiting in the recovery room was noted by nurses unaware of group assignments. Hemodynamic data was analyzed using ANOVA technique.

Results: A statistically significant decrease in mean hr was observed in groups 1 and 2 after administration of alf. No significant changes in mean heart rate from baseline were observed at any time in groups III or IV. Statistically significant but clinically insignificant decreases in bp were noted in groups I and II after administration of alf (Fig 1 C,D). These changes were transient and disappeared after intubation. A significant increase in bp was observed in group I after receiving surgical stimulation (Fig 1G). Patients in group I not receiving halo as part of the maintenance anesthetic were extubated and alert in a significantly shorter time than the other groups (Table).

Discussion: Alf, when used at these doses in children, produces an acceptable degree of hemodynamic stability but may require a higher initial dose or a continuous infusion to blunt reponse to surgical stimulation. The use of alf permits a more rapid return to an alert state in children when compared to halo, a finding in agreement with adult studies.[1]

Reference: 1. Anaesthesia 39:1202-1206, 1984.

Figure 1



TABLE

Group n	Alertness min ± SD	Extubation min ± SD	Vomiting n	%
I (19)	10±9*	3±2*	10	(53)
II (20)	21±11	6±2	11	(55)
III (20)	25±11	8±4	9	(45)
IV (21)	24±12	8±3	4	(19)

* Denotes p<0.05 when compared to the group

S194

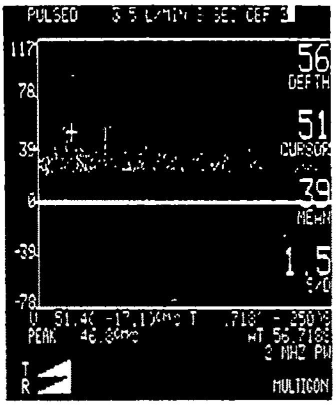
TRANSCRANIAL DOPPLER VERIFICATION OF PULSATILE CEREBRAL BLOOD FLOW DURING CARDIOPULMONARY BYPASS

John M Murkin MD,FRCPC; Don H Lee MD,FRCPC

Departments of Anaesthesia and Neuroradiology, University Hospital, University of Western Ontario, London, Ontario

Clinical studies of the influence of pulsatile perfusion on the functioning of various organ systems during cardiopulmonary bypass (CPB) have been controversial and inconsistent.[1] This is in part due to an inability to readily verify transmission of pulsatile waveforms in various organs. We assessed the influence of both pulsatile and nonpulsatile perfusion during hypothermic CPB on middle cerebral artery flow velocity (MCA-FV) using a MULTIGON^{R} transcranial doppler. **METHODS:** With institutional approval, 5 patients undergoing hypothermic CPB (NPT 26-28°C) using a Cobe-Stockert^{R} pump, Bard 5700^{R} hollow fibre membrane oxygenator, Intersept^{R} 20 micron arterial line filter and Argyle 21-24 arterial cannula, were perfused at flows of 2.0-2.5 $L.m^{-2}.min^{-1}$ using a COBE Flow Controller II^{R} pulse generator at an average frequency of 80 bpm. Prior to commencement of CPB, MCA was identified through the left temporal window using a MULTIGON 500V TCD 2 MHZ pulsed Doppler velocimeter at depth 4.5-5.5 cm producing optimal insonation. With establishment of stable pulsatile perfusion at nasopharyngeal temperature (NPT 26-28°C) MCA-FV was measured. **RESULTS:** At NPT 27.4±1.3 °C, hemoglobin 7.2±0.9 g/dl, and systemic pulse pressure 35±15 mmHg, average peak/mean MCA-FV (DMCA-FV) was 8.7±2.0 cm/s at peak MCA-FV 38.2±8.2 cm/s; a mean 30.5±8.2% phasic increase in MCA-FV. **DISCUSSION:** We believe this study represents the first in vivo demonstration of transmission of a CPB-generated pulsatile waveform into the brain in patients during hypothermic CPB (see Fig.1). TCD assessment of end-organ perfusion characteristics promises to be an important technique for further investigating the pathophysiology of CPB. **REFERENCES:** Hickey PR, Buckley MJ, Philbin DM. Pulsatile and nonpulsatile cardiopulmonary bypass: review of a counterproductive controversy. Ann Thorac Surg 1983;36:720-37.

Fig 1. Phasic increase in MCA-FV with pulsatile perfusion during hypothermic CPB.



S195

TITLE: MYOCARDIAL OXYGENATION AND ISCHEMIA IN HYPERTENSIVE PATIENTS UNDERGOING CORONARY REVASCULARIZATION

AUTHORS: JT Murphy MD, EA Moffitt MD, RI Hall MD, RW Landymore MD, JAP Sullivan MD, and JR Wood MD.

AFFILIATION: Depts of Anaesthesia and Surgery, Dalhousie University and Maritime Heart Centre, Halifax, NS, Canada B3H 2Y9

INTRODUCTION: The purpose was to determine whether a difference in myocardial oxygenation and ischemia occurred in hypertensive patients randomly receiving sufentanil (S), fentanyl (F), enflurane (E), and isoflurane (I) anesthesia for coronary revascularization.

METHODS: With institutional approval and informed consent, 34 patients with treated hypertension were studied (preop mean arterial pressure (MAP)=96 mmHg, LVEDP=13 mmHg, EF=65%, NYHA III=26 and IV=6). Cardiac medications: Beta-blockade in 27, Ca^{++} entry blockade in 32. They received pancuronium 0.1 $mg.kg^{-1}$ and: 1- S 4 ug/kg (induction-IND) + E (maintenance-M) (n=8); 2- F 30 ug/kg (IND) + E (M) (n=10); 3- S 4 ug/kg (IND) + I (M) (n=8); or 4- S 6 ug/kg (IND) + S 1.44 $ug.kg^{-1}.min^{-1}$ (M) (n=8). Serial studies were performed at 8 points from preinduction (control) to 1 hour postop. Hemodynamic and coronary sinus blood flow[1] measurements were performed. Myocardial oxygen consumption (MVO_2) and myocardial lactate production (MLP) values were calculated.[1] EKG lead V5 was monitored intraop. Analyses of covariance and variance determined differences ($p<0.05$) within and between each group.

RESULTS: There were no differences between groups in demographics or in duration of anesthesia, cardiopulmonary bypass (CPB), aortic cross-clamping and postop ventilation. There were no differences in hemodynamics except for lower pulmonary capillary wedge pressure (PCWP) and right atrial pressure in group 3 post-CPB. MAP, stroke work index and PCWP were maintained at levels significantly lower than control in all groups. Coronary sinus oxygen content was greater in groups 3 and 4 at induction and intubation. Ischemia: 23/34 had preop ST-T abnormalities on the 12-lead EKG. At control 9/34 had ST depression > 1mv; 4/34 had **MLP**. Intraop: 15/34 had ST depression (>1mv) pre-CPB and 16/34 post-CPB. **MLP (ischemia)** was seen at least once in 11/34 pre-CPB and 16/34 post-CPB. Postop: 31/34 had ST/T changes, 4/34 had nonfatal myocardial infarctions, 1/34 died (4 hours postop, group 4).

DISCUSSION: Induction with S or F and maintenance with E, I, or S (infusion) had similar effects on myocardial oxygenation. A high incidence of ischemia occurred intraop and postop, associated with preop EKG abnormalities compatible with ischemia.

REFERENCE: 1. Anesth.Analg. 1986;65:395-410.

S196

TITLE: COMPARATIVE CARDIOVASCULAR DEPRESSION OF HALOTHANE AND ISOFLURANE IN NEONATES

AUTHORS: D.J. Murray, M.D., R.B. Forbes, M.D., L.T. Mahoney, M.D.

AFFILIATION: Department of Anesthesia, University of Iowa College of Medicine, Iowa City, IA 52242

Introduction: Comparative neonatal cardiovascular studies during halothane and isoflurane anesthesia have been limited to measurements of blood pressure and heart rate.[1,2] The purpose of this study was to measure as well as compare cardiovascular changes at equal MAC halothane and isoflurane concentrations in neonates.

Methods: Two-dimensional and pulsed Doppler echocardiography (Hewlett-Packard Sonos 500) were used to measure left ventricular dimensions and pulmonary artery blood flow velocity in 19 neonates. The echocardiographic data as well as blood pressure and heart rate were recorded prior to anesthesia induction.

Following mask inhalation anesthesia induction with end-expired halothane (n=10) and isoflurane (n=9) concentrations maintained at 1.0 MAC cardiovascular measures were repeated. At 1.5 MAC end-expired concentrations, a second set of cardiovascular measures were recorded during anesthesia. A final set of cardiovascular data was collected two minutes following intravenous atropine (0.02 mg.kg-1). All measurements were completed prior to intubation and skin incision. Results were analyzed using two way analysis of variance and are expressed as mean ± SD.

Results: Mean blood pressure, cardiac output, stroke volume and ejection fraction declined similarly and significantly from awake values at 1.0 MAC and 1.5 MAC halothane and isoflurane respectively (Table 1). Heart rate (HR) decreased significantly at 1.5 MAC halothane in neonates. Cardiac output increased following atropine; but, SV and EF remained unchanged.

Discussion: The decreases in mean blood pressure, stroke volume, ejection fraction and cardiac output are of greater magnitude than reported in prior clinical studies of older infants and small children (mean age = 12 mos).[3]

In neonates, halothane and isoflurane produce similar cardiovascular depression at 1.0 MAC and 1.5 MAC.

References:
1. Lerman J, et al: Anesthesiology 1983;59:421-424.
2. Cameron CB, et al: Anesth Analg 1984;63:418-420.
3. Murray DJ, et al: Anesthesiology 1987;67:211-217.

	Awake	1.0 MAC	1.5 MAC	1.5 MAC + Atropine
Heart Rate ($beats.min^{-1}$)				
Halothane (n=10)	144 ± 15	143 ± 13	134 ± 16*	153 ± 10*
Isoflurane (n=9)	152 ± 13	152 ± 29	154 ± 23	177 ± 17*
Cardiac Output ($1.min^{-1}$)				
Halothane (n=10)	0.82±0.27	0.60±0.20*	0.48±0.18*	0.57±0.16*
Isoflurane (n=9)	0.94±0.34	0.69±0.19*	0.64±0.18*	0.87±0.31
Stroke Volume (ml.beat)				
Halothane (n=10)	5.7 ± 2.0	4.2 ± 1.4*	3.6 ± 1.1*	3.8 ± 1.2*
Isoflurane (n=9)	6.1 ± 2.4	4.7 ± 1.4*	4.3 ± 1.7*	4.9 ± 1.7*

Results are mean ± SD: *$p < 0.05$ from awake

S197

TITLE: COMPARISON OF HEMODYNAMIC RESPONSE TO CARDIOVERSION WITH METHOHEXITAL AND ETOMIDATE

AUTHOR: M. NAKATSUKA, M.D.
AFFILIATION: MEDICAL COLLEGE OF VIRGINIA, RICHMOND VIRGINIA 23298

INTRODUCTION: Anesthetic drugs such as methohexital and etomidate have been used to facilitate cardioversion (1). Patients who require cardioversion usually have significant cardiac disease. Therefore, we investigated the change in cardiac output and hemodynamic response to cardioversion with methohexital and etomidate using thoracic electrical bioimpedance (TEB).

METHOD: After institutional review committee approval, 13 patients with cardiovascular disease and atrial fibrillation participated in this study. Six patients received methohexital, and seven patients had etomidate. Following pre-oxygenation for 3 min., anesthesia was induced with etomidate (0.2 mg/kg) or methohexital (1-1.5 mg/kg). Patients were monitored with a pulse oximeter, ECG, automated blood pressure machine (Dinamap) and TEB. Cardiac output and ejection were measured with TEB. Systolic blood pressure (SBP), cardiac output (CO), and ejection fraction (EF) were recorded immediately before and after cardioversion, 2 min. and 5 min. after cardioversion, and after recovery. Duration of apnea and recovery time were recorded. Recovery was assessed by response to verbal command and ability to recall the location. Data were analyzed using a paired t test, and $p<0.05$ was accepted as a significant difference.

RESULTS: The duration of apnea was significantly shorter with etomidate (16 ± 12 seconds) than with methohexital (40 ± 20 seconds) ($p<0.05$). However, recovery time was faster with methohexital (8 ± 2 min) than with etomidate (13 ± 2 min) ($p<0.05$). Because both duration of apnea and recovery time were quite short, these results were clinically insignificant. There were no significant changes in CI and EF during the course of cardioversion with etomidate or methohexital.

DISCUSSION: Methohexital and etomidate have been the most popular agents in this institution for induction of anesthesia for cardioversion. Although etomidate had a shorter apnea time and longer recovery time than methohexital, they showed no clinically significant difference. Both agents maintained stable cardiac output and ejection fraction during the entire course of cardioversion. SBP increased significantly in 5 min and after recovery with both agents. We conclude that methohexital and etomidate are safe anesthetic agents for cardioversion even for patients with significant cardiac diseases.

REFERENCE
(1) Valtoner, M., Kanto, J., Klossner, J.: Anesthesia for cardioversion: a comparison of propofol and thiopeatone. Can J Anesth., 1988, 35, 479-83.

S198

Title: HEMODYNAMIC AND RESPIRATORY EFFECTS OF TRANSTRACHEAL HIGH FREQUENCY JET VENTILATION DURING DIFFICULT INTUBATION.

Authors: M. Nakatsuka, M.D. and R. Campbell, D.D.S.
Affiliation: Department of Anesthesiology, Medical College of Virginia, Richmond, Virginia

INTRODUCTION: High frequency jet ventilation has been successfully used to ventilate patients in respiratory failure. We investigated cardiac output and respiratory effects of percutaneous transtracheal HFJV during difficult intubation using fiberoptic bronchoscopy under general anesthesia.

METHOD: With informed consent and approval from the Institutional Review Committee, eight patients with a difficult airway were studied using transtracheal HFJV. A 13 gauge cricothyroidotomy jet ventilation cannula was inserted percutaneously through the cricothyroid membrane under local anesthesia. Anesthesia was induced with Etomidate, Alfentanil and Vecuronium. HFJV was started with 100% oxygen at 30-35psi of driving pressure, 100 cycles per minute, and inspiratory/expiratory ratio of 25%. Thoracic electrical bioimpedance (TEB) was used to measure continuous cardiac output. Mean blood pressure (MBP), heart rate (HR), cardiac index (CI), and ejection fraction (EF) were measured before induction of anesthesia, 1 min HFJV, 5 min HFJV, 10 min HFJV, and following fiberoptic intubation with continuous positive pressure ventilation. Data were analyzed with paired t-test and $p<0.05$ indicated statistical significance. Values are expressed ± SD.

RESULTS: Hemodynamic data are summarized in Table 1. The results of arterial blood gases are shown in Table 2. There were no significant changes in HR, CI and EF. PaO_2 significantly increased with 10 min HFJV. $PaCO_2$ tended to increase with 10 min HFJV.

DISCUSSION: We demonstrated stable hemodynamic conditions as well as satisfactory pulmonary gas exchange during transtracheal HFJV under general anesthesia. We believe percutaneous transtracheal HFJV and fiberoptic bronchoscopy can be safely used to manage patients with a difficult airway and intubation under general anesthesia.

TABLE 1: HEMODYNAMIC DATA

	Pre Induction	HFJV 1 min	HFJV 5 min	HFJV 10 min	After Intubate
HR	68±12	58±13	50±12^{+}	50±11^{+}	55±10^{+}
BP	97±6.3	74±11	74±7.7	71±5.5*	75±12
CI	2.3±0.5	2.1±0.3^{+}	2.4±0.3	2.2±0.3^{+}	2.3±0.4
EF	46±5.7	52±3.6	53±2.5	50±4.0	59±1.0^{+}

$^{+}p < 0.05$ $^{*}p < 0.01$

TABLE 2: ARTERIAL BLOOD GAS

	Pre-induction	10 min HFJV
pH	7.35±0.03	7.31±0.05
$PaCO_2$	39±1.4	42±3.8*
PaO_2	85±17	240±91*

$^{*}p < 0.05$

S199

Title: RELIABILITY OF AN OBJECTIVE PAIN SCALE IN CHILDREN

Authors: J Norden, MSN, R Hannallah, MD, P Getson, PhD, R O'Donnell, BA, G Kelliher, BSN, N Walker, BSN
Affiliation: Children's National Medical Center, Washington, DC 20010

The objective assessment of pain intensity in children is difficult. Infants and young children express pain differently depending on their developmental level as well as chronological age. Recently, several Objective Pain Scales (OPS), which measure both physiologic and behavioral responses to pain, have been utilized to quantify postoperative pain in children. This study examines interrater agreement, interrater reliability and internal consistency of items and scale for a frequently used OPS.[1-3]

Methods: The institutional review committee approved the protocol and waived the requirement of parental consent. Thirty ASA PS I infants and children ages 8 months to 13 years were studied in the PACU. Three observers, trained in the use of the OPS, simultaneously evaluated each patient for ten second periods and provided independent OPS ratings. The three scores from each observation were compared by using an agreement index, Kappa statistics for interrater reliability, and coefficient alpha for internal consistency.

Results: Mean interrater agreement for all observations was 97.3%, ± 9.1 SD (table). Kappa statistics calculated for each item separately ranged from .71 to .95. Coefficient alpha was .986 for one rater and .983 for the other two raters.

OPS Scale Item[1-3]	% Rater Agreement	Item-Total Correlations
BP Change	100.0	.54
Crying	96.7	.91
Movement	96.7	.87
Agitation	97.8	.90
Verbal expression	95.6	.67

Discussion: This Objective Pain Scale has been very useful in measuring pain in children and non-verbal infants. However, reliability testing including the accuracy of the rating or consistency of the instrument items when used by different observers has not previously been documented. This study indicates that the OPS is a reliable instrument that can be used by different trained observers for the objective assessment of postoperative pain in pediatric patients.

REFERENCES:
1. Anesthesiology 1987; 66:832-834.
2. Anesthesiology 1988; 69:102-106.
3. Anesthesiology 1988; 69:A770.

S200

TITLE: PREOPERATIVE RESPIRATORY MONITORING IN THORACIC PATIENTS

AUTHORS: PH Norman MD, MD Daley MD, AN Sandler MB
AFFILIATION: Anesth. Dept., Toronto General Hospital, University of Toronto, Toronto, Canada

INTRODUCTION: Sedated and post-operative patients are susceptible to hypoxaemia and apneas.[1,2] Also, normal patients and those with COPD may exhibit disordered breathing and desaturation during normal sleep.[3] This study was designed to determine the frequency of *preoperative* respiratory problems in thoracic patients.

METHODS: Data was reviewed from 62 (36M,26F) ASA 1-3 thoracic surgery patients previously included in our epidural narcotic studies (with ethics approval). Patients with sleep apnea syndrome (SAS) or severe COPD had been excluded. All patients were studied the night prior to planned surgery using respiratory inductance plethysmography (RIP). Continuous pulse oximetry (SpO$_2$) was obtained on 49 of the patients, 61 had arterial blood gases (ABG) taken prior to the monitoring period and 49 had in-dwelling arterial lines through which ABG's were taken every 2 hours. RIP data were analyzed for respiratory rates (RR), slow respiratory rates (SRR; RR<10bpm) and apneas (AP; Vt<100ml for ≥15sec).

Data are expressed as mean ± 1 standard deviation. The Mann-Whitney rank-sum test and ANOVA were used where appropriate. A p value ≤0.005 was considered statistically significant (Bonferroni correction).

RESULTS: Subjects had a mean age of 58±12 years, percent ideal body weight of 114±18% and FEV1/FVC% of 65±11%. Forty-six patients had ≥1 AP, 30 had ≥1 AP/hr and 12 met criteria for SAS (≥5 AP/hr). SRR's were present in 20 with a lowest RR of 3/min. The lowest SpO$_2$ was 62% and lowest PaO$_2$ was 47mmHg. The maximum decrease in SpO$_2$ was 27% from the preceding 5 minute baseline. The lowest PaO$_2$, SpO$_2$ or maximum decrease in SpO$_2$ did not coincide with an AP or SRR. The highest PaCO$_2$ was 54mmHg. There was no difference in minimum SpO$_2$, SRR, or number of AP between subgroups divided on the basis of sex, smoking, planned operation, clinical COPD, FEV1/FVC%, or ABG's. The 2-hourly ABG's did not allow prediction of occurrence, frequency or severity of desaturations.

The percentage of time spent in AP correlated with the percentage of time spent in SRR ($p<0.001$). The maximum decrease from baseline SpO$_2$ during an AP correlated with the minimum SpO$_2$ observed for that patient during an AP and with the percentage of time in SRR or AP ($p=0.001$).

DISCUSSION: Thoracic patients have episodes of AP, SRR and desaturation during the night prior to surgery. None of the usual clinical criteria allow prediction of which patients will have these abnormalities. ABG do not reliably indicate the presence or extent of intermittent desaturation. Any study that concludes that a certain treatment predisposes patients to intraoperative or postoperative breathing abnormalities or oxygen desaturation without monitoring the same patients preoperatively may be in error.

REFERENCES:
1. Anesthesiology 1989; 71:A1088.
2. Anesthesiology 1985; 63:20-28.
3. Am Rev Resp Dis 1978; 118:909-939

S201

Title: INTRAOPERATIVE MEASUREMENT OF APTT AND PT BY PORTABLE LASER PHOTOMETER

Authors: G.A. Nuttall, M.D.; W. Oliver, M.D.; F.M. Beynen, M.D.; J.J. Dull, CRNA; M.J. Murray, M.D.; W.L. Nichols, M.D.
Affiliation: Mayo Clinic, Rochester, MN 55905

Introduction: The rapid assessment of coagulation status following cardiopulmonary bypass (CPB) is important. A whole blood system (Ciba Corning 512 Coagulation Monitor) has been developed for rapid measurement of the prothrombin time (PT) and activated partial thromboplastin time (APTT). In this investigation, PT and APTT from the Ciba monitor were compared with reference lab plasma PT and APTT following CPB. The effect of sample sites, and the influence of hemoglobin (Hgb) concentration and platelet (PLT) count on the accuracy and precision of the Ciba monitor were also evaluated.

Methods: Following institutional review board approval and patient informed consent, we examined 100 patients undergoing CPB. A #20 radial arterial catheter and a right atrial (RA) catheter were placed intraoperatively. PT, APTT, and complete blood count were obtained from the arterial catheter 10 min following protamine administration using the standard hospital lab. From the same arterial sample and from a RA sample, the APTT and PT were measured using the Ciba monitor.

Results: The arterial Ciba APTT and PT had 0.95 and 0.77 correlation coefficients with the lab arterial APTT and PT, respectively ($p<0.01$) (Fig. 1 and 2). The Ciba monitor provided APTT and PT results in less than 3 min in comparison to 45 min for the hospital lab. The RA catheter Ciba PT and APTT had a correlation coefficient of 0.59 and 0.63 with the lab PT and APTT, respectively ($p<0.01$). The correlation coefficients of the Ciba PT and APTT with Hgb concentration and PLT count were all less than 0.3.

Discussion: The Ciba monitor provides APTTs that are comparable and accurate with respect to the lab APTTs. The Ciba monitor PT, though not as accurate, could be used as an approximation of the lab PT. RA blood samples for determination of PT and APTT with the Ciba monitor were associated with less accuracy. The accuracy of the monitor was not affected by a variation of Hgb concentration and PLT count between 6-12 gm/dl and 15-300 10^9/L, respectively.

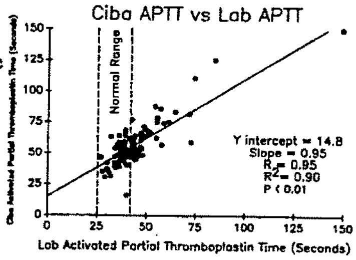


Fig. 1

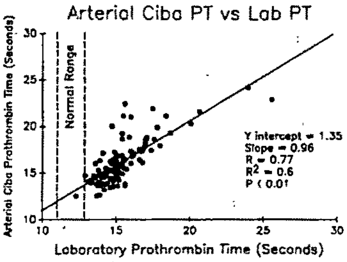


Fig. 2

S202

Title: BUTORPHANOL: A NARCOTIC FOR DAY-CARE PEDIATRIC SURGERY

Authors: HV O'Brien, MD, WM Splinter, MD
Affiliation: Department of Anaesthesia, Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, Ontario, Canada

Introduction: Butorphanol (B) is an opiod analgesic with agonist-antagonist effects. It is effective in the management of adult postoperative pain and associated with fewer side effects, such as vomiting and respiratory depression.[1,2] We compared B to equipotent morphine (M) to determine the efficacy of this narcotic in children undergoing minor surgery.

Methods: With parental consent and Hospital Ethics Committee approval we studied 110 healthy children of ages 18 months to 13 years undergoing elective repair of inguinal hernias or undescended testicles. After induction of anesthesia with halothane or 5 mg/kg thiopental, the subjects were administered a standardized anesthetic which included 1.5% halothane, 0.1 mg/kg vecuronium and 25 mcg/kg droperidol, tracheal intubation and mechanical ventilation. One minute after tracheal intubation, the children were given 150 mcg/kg M or 30 mcg/kg B following a randomized, stratified, blocked and double-blind design. At the end of the operation, gastric contents were evacuated with an orogastric tube, the patients were given 50 mcg/kg neostigmine and 20 mcg/kg atropine and the tracheal tube was removed after resumption of spontaneous breathing and before airway reflexes returned. The patients were followed for 4 hours after their operation. The time required to recover from the anesthetic was recorded, vomiting was recorded, in the recovery room children's pain was objectively assessed with a modified CHEOPS pain score[3] and analgesics were administered when indicated, and the length of time before administration of oral analgesics on the ward or in the Day-Care Surgical Unit was recorded. Data was analyzed using Chi Square, ANOVA, ANCOVA, Fisher Exact, and Kruskal-Wallis tests where appropriate. The acceptable alpha error was set at 5%.

Results: B was administered to 55 patients. Seventy-six had inguinal hernia repairs and 34 had an orchidopexy. Forty-two children had an IV induction. There was no difference between the groups with respect to age, weight, length of surgery, or intraoperative blood pressure. The B-subjects had a lower pain score 10 minutes after arrival in the recovery room, and a reduced incidence (15%) of post-operative vomiting (M-treated patients had a 35% incidence), $P=0.02$. B-subjects had a slightly longer recovery room stay (65.4 vs 60.2 minutes, $P= 0.03$). Two patients required an unscheduled admission to hospital after their operation because of vomiting. Both of these patients were given M intraoperatively. The incidence of vomiting was less among the subjects who underwent orchidopexy vs. hernia repair (6% vs 32%), $P<0.01$.

Discussion: B is not an ideal narcotic, but it has significant advantages over M in the population studied. B-subjects had a slight delay in discharge from the recovery room and a small decrease in pain, but these are of minor concern when compared to the marked decrease in vomiting after surgery associated with Butorphanol.

References: 1. Acute Care 1986; 12(Suppl 1): 2-7.
2. Int J Gynaecol Obstet 1980; 18: 363-367.
3. Adv Pain Res Ther 1985; 9: 395-402.

S203

TITLE: MONITORING OF LEFT VENTRICULAR TRANSMURAL PRESSURE IN ACUTE CARDIAC TAMPONADE

AUTHORS: S. Ohara, M.D., K. Goto, M.D.,
R.L. Torline, M.D., H. Goto, M.D.,
K. Arakawa, M.D., Ph.D.
AFFILIATION: Anes.dep., University of Kansas,
Kansas City,Kansas 66103

This study was approved by the institutional animal care. Cardiac tamponade can be a life-threatening complication after open-heart surgery. Pulsus paradoxus or increasing central venous pressure (CVP) is not sensitive and specific in detecting increases in intrapericardial pressure (IPP). In clinical medicine pulmonary capillary wedge pressure (PCWP) is frequently used to assess left ventricular (LV) preload. However, in patients with cardiac tamponade it is obvious that the elevated PCWP does not necessarily reflect an increase in LV preload. To obtain a better estimate of LV preload, it would be desirable to measure LV transmural diastolic pressure (LTMP). IPP, however, is not easily measured in patients. It has been reported that IPP and right atrial pressure (RAP) tended to be similar (1). The study suggests that PCWP-CVP gradient may be useful indirect estimates of LTMP in the cardiac tamponade.

Mongrel dogs were anesthetized with pentobarbital and normally ventilated with oxygen. Left atrial pressure (LAP), RAP, CVP, PCWP, and cardiac output were measured. IPP was measured with a flat liquid-filled balloon catheter placed in the pericardial space. After left thoracotomy incision was closed and steady state has been established, mean values of hemodynamic parameters were recorded at end-expiration while increasing IPP by continuous infusion of normal saline (5 ml/min) into the pericardial space.

RAP increased progressively with increasing severity of cardiac tamponade, and accurately reflected IPP (Fig. 1). There was a significant positive correlation between LTMP (LAP-IPP) and stroke volume index (SVI) (Fig. 2). Gradients of PCWP minus CVP (Pw-c) reflect LTMP considerably well (Fig. 3). Fig. 4 showed a negative correlation between changes of IPP (ΔIPP) and Pw-c. The data from Fig. 4 were analyzed using the contingent table analysis. If Pw-c is under 2 mmHg, ΔIPP beyond 2 mmHg can be detected significantly ($p<0.01$).

In summary, reduction in left ventricular transmural pressure represented by PCWP-CVP gradient is sensitive to increasing intrapericardial pressure, and the early stage of cardiac tamponade may be suspected.

Reference:1. Circulation 73:428-432, 1986

Fig. 1

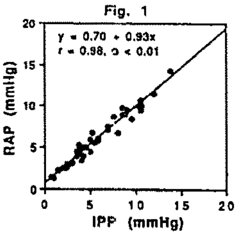


Fig. 2

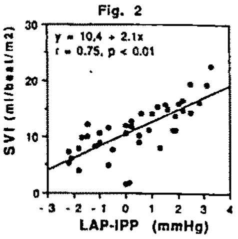


Fig. 3

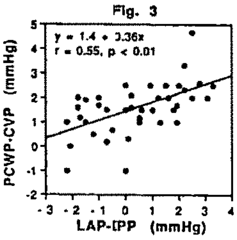
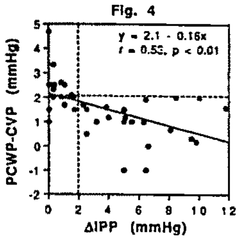


Fig. 4



S204

TITLE: DOSE-RESPONSE RELATIONSHIP OF ORAL CLONIDINE IN TETRACAINE SPINAL ANESTHESIA

AUTHORS: K.Ohta, M.D., I.Takahashi,M.D., H.Iwasaki, M.D., M.Matsumoto,M.D., A.Namiki,M.D.
AFFILIATION: Anes. Dept., Sapporo Medical College,
Sapporo, Japan 060

INTRODUCTION: Intrathecal clonidine has been shown to prolong tetracaine spinal anesthesia in humans (1). Recently it was reported that oral clonidine was able to prolong the duration of bupivacaine spinal anesthesia (2). However the effect of oral clonidine in tetracaine spinal anesthesia is unknown. This study was designed to assess the effect of oral clonidine premedication in tetracaine spinal anesthesia.

METHODS: Forty-eight ASA I patients scheduled for urological procedure under spinal anesthesia were studied after informed consent and institutional approval. They were divided randomly into 4 groups. The following premedication was given 1 hour before surgery; group I, oral triazolam 250 ug; and groups II, III and IV, oral clonidine 75 ug, 150 ug and 300 ug, respectively. All patients were given spinal anesthesia with isobaric 0.5% tetracaine 3 ml. The level of sensory blockade was evaluated by pin-prick. The level of sensory blockade was studied every 15 minutes until the pin-prick analgesia recovered to L2 segment. Blood pressure and heart rate were recorded every 5 minutes. ANOVA and Scheffe F-test were used for statistical analysis.

RESULTS: Patients in the 4 groups were comparable for mean age, weight and height. Features of sensory blockade are shown in table 1. Initial values and changes in blood pressure were similar in the 4 groups. Initial values of heart rate were lower in group IV compared to group I.

DISCUSSION: Our findings demonstrated that oral clonidine premedication prolonged tetracaine spinal anesthesia. In respect to the relationship between the clonidine dose and the duration of sensory blockade, a plateau was reached at a clonidine dose of 150 ug with no additional effect for a 300 ug dose.

REFERENCES:
1. Anesth Analg 68: 619-622, 1989
2. Acta Anaesthesiol Scand 33: 137-141, 1989

Table 1. Features of sensory blockade

	GROUP I (n=13)	GROUP II (n=12)	GROUP III (n=12)	GROUP IV (n=11)
HIGHEST LEVEL OF SENSORY BLOCKADE	T7.6 ±1.7	T6.8 ±1.9	T7.9 ±1.8	T7.8 ±0.8
TIME FOR 2 SEGMENT REGRESSION (min)	78 ±15	$125^{a)}$ ±29	$169^{a,b)}$ ±24	$153^{a)}$ ±30
TIME FOR 4 SEGMENT REGRESSION (min)	122 ±19	$185^{a)}$ ±50	$279^{a,b)}$ ±48	$233^{a)}$ ±36
TIME FOR REGRESSION TO L1 (min)	160 ±41	$233^{a)}$ ±32	$308^{a,b)}$ ±31	$288^{a)}$ ±41

All values are mean±SD. a) $P<0.01$ vs GROUP I
b) $P<0.01$ vs GROUP II

S205

TITLE: **DETECTION OF MYOCARDIAL ISCHEMIA DURING SUSPENSION MICROLARYNGEAL SURGERY**

AUTHORS: MA Olympio, MD, WK Haisty, MD, O Pahlm, MD, JA Koufman, MD, DB Weeks, MD

AFFILIATION: Depts. of Anesthesia, Otolaryngology, and Medicine, Wake Forest University Medical Center, Winston-Salem, NC 27103, & Dept. of Clinical Physiology, University Hospital, Lund, Sweden

INTRODUCTION: Computer-augmented analysis of serial 12-lead ECGs obtained on a Mortara Instrument Electrocardiograph (Milwaukee, WI) can be used to detect transient ST-T wave changes not observed by conventional CS_5 leads (1). We used this device in a pilot study to detect myocardial ischemia during suspension microlaryngeal surgery (SMLS), a procedure known for its potential myocardial complications (2).

METHODS: Seventeen consecutive patients age ≥40 and without a history of CHF were prospectively studied under IRB approval, which did not require informed consent. Preoperative systolic blood pressures were averaged (avSBP) and hypertension (HTN) was defined as 120% x avSBP; tachycardia (TACH) was defined as >100bpm. Standard bipolar CS_5 (three lead) ECG was used and the Mortara Instrument was set at one-minute intervals to collect 12-lead ECG data for subsequent analysis by cardiologists. Protocol anesthesia included fentanyl-droperidol-methohexital-succinylcholine during jet venturi ventilation after thiopental induction; labetalol was used to control both HTN and TACH, propranolol for TACH alone, or nitroglycerine for HTN alone. Tight hemodynamic control was attempted while the anesthesiologist observed the CS_5 lead for ST-T wave changes. Blinded to the event, the cardiologists later computer-analyzed the Mortara data for ischemia by pre-defined ST-T criteria. The incidence of ischemia by type of monitor was compared using McNemar's test. Mean maximum heart rates±SD were compared by two-tailed t-testing.

RESULTS: Table 1. Fourteen patients were managed by protocol; none had ischemia by intraoperative CS_5, but two did by Mortara. Three patients had protocol violations by receiving volatile anesthetics, lower fentanyl-droperidol dosages, and significantly less control of heart rates compared to protocol patients (138±23 vs 109±12, $p<0.005$); two had ischemia by CS_5 and all three had ischemia by Mortara. Overall, the five episodes of ischemia occurred at maximum heart rate. Postoperative ECG revealed no evidence of infarction in any patient.

DISCUSSION: Though not significant by McNemar's test, our results support the hypothesis that computer-analyzed serial 12-lead electrocardiograms detect myocardial ischemia during SMLS more frequently than careful observation of a single bipolar CS_5 lead, and that the incidence of ischemia may be high (29%). The association among tachycardia, anesthetic management, and the frequency of ischemia in SMLS patients calls for a randomized, controlled study using this sensitive, non-invasive device.

REFERENCES:

1. Krucoff MW: Am J Cardiol 1990;65:143-148.
2. Strong MS, et al: The Laryngoscope 1974; LXXXIV: 908-920.

Table 1. Detection of ischemia by type of monitor and anesthetic. Mean maximum heart rates ± SD by anesthetic technique.

	Protocol (n=14)	Non-Protocol (n=3)
CS_5	0	2
Mortara	2	3
Heart rate	109±12	138±23

S206

TITLE: THIOPENTONE AND PROPOFOL IN OBSTETRICS: EFFECTS ON THE FETOPLACENTAL CIRCULATION. PRELIMINARY STUDY.

AUTHORS: Orr DA MB, Iftikhar M MB, Beattie RB MD, Bill KM MB, Thompson WB MD & Moore J PhD.

AFFILIATION: Departments of Anaesthetics and Obstetrics, The Queen's University of Belfast, Northern Ireland.

INTRODUCTION. Several studies[1,2] have investigated propofol (2,6 diisopropylphenol) as an induction agent for use in elective Cesarean section. Compared with thiopentone it causes relative hypotension, although wakening is more rapid and emetic effects are less. The aim of this study was to investigate the effects (if any) on the fetoplacental circulation occurring at induction of anesthesia.

Changes in uterine blood flow can cause alterations in fetal placental resistance which in turn affect umbilical artery blood velocity. Continuous Doppler ultrasound is used in obstetric practice[3] to record umbilical artery velocity waveforms (UAVW), it has been found that pulsatility index (PI) (systolic-diastolic/mean wave heights) is a good indicator of changes in placental resistance, such as those occuring in pre-eclampsia.

METHODS. Following University Ethical Committee approval, 10 consenting healthy term patients presenting for elective Cesarean section were randomly allocated to receive either thiopentone or propofol. After premedication with omeprazole they were brought to the operating room, where intravenous cannulation was performed and monitoring began. Continuous wave Doppler ultrasound (Doptek 9000) was used to locate the UAVW non-invasively through the anterior abdominal wall. Non-invasive blood pressure, end tidal CO_2, arterial oxygen saturation and EKG were measured continuously, the displays of the above monitors were filmed using a video 8 TV camera and recorded on videotape. The output from the Doptek 9000 was recorded onto the sound channel of this videotape. This technique allows offline analysis of several continuously changing variables.

After at least 5 minutes of baseline recording and preoxygenation, anesthesia was induced with either thiopentone (4 mgs kg^{-1}) or propofol (2 mgs kg^{-1}). Induction was followed by a 2 minute recording period, during which no other drugs were given, ventilation was assisted if apnea occurred. Intubation was facilitated with suxamethonium 100 mgs, and anesthesia continued with N_2O, isoflurane (0.75%) and atracurium. Maternal blood sampling for norepinephrine levels was performed. Ultrasound recordings were stopped when the obstetrician started skin preparation. Neonatal well-being was assessed with cord blood gas analysis and neurobehavioural scoring.

RESULTS. Demographic data was similar for both groups. At induction maternal systolic blood pressure fell 5.6 mmHg with propofol, but rose 3.6 mmHg with thiopentone, diastolic pressures fell by 14.2 & 7.8 mmHg respectively there was no statistically significant intergroup difference. Maternal heart rate was higher after thiopentone.

Analysis of ultrasound recordings showed no differences in PI, S/D ratio, resistance index or fetal heart rate, either with respect to time or between groups (repeated measures ANOVA). There was no difference in neonatal outcome.

DISCUSSION. This preliminary work has not demonstrated any deleterious effects of propofol as compared to thiopentone, when used in elective obstetric anesthesia. This methodology may be useful in further work.

REFERENCES.

1. Moore J et al. Anaesthesia 44(9):753-757,1989
2. Valtonen M et al. Anaesthesia 44(9):758-762,1989
3. Beattie RB, Dornan JC.BMJ 298(6674):631-635,1989

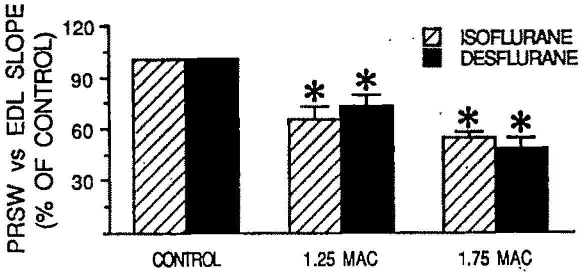
S207

Title: EFFECTS OF DESFLURANE AND ISOFLURANE ON MYOCARDIAL CONTRACTILITY IN CHRONICALLY INSTRUMENTED DOGS

Authors: PS Pagel, MD, WT Schmeling, MD, PhD, JP Kampine, MD, PhD and DC Warltier, MD, PhD
Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

The effects of desflurane (D) and isoflurane (I) on myocardial contractility were compared using the preload recruitable stroke work (PRSW) versus end diastolic length (EDL) relationship, a linear afterload-insensitive index of contractile function in conscious[1] and anesthetized[2] dogs.

With prior approval of the Institutional Animal Care Committee, mongrel dogs (N=7) were anesthetized and instrumented for measurement of aortic blood pressure, left ventricular pressure, +dP/dt and cardiac output. Regional contractility (%SS) was assessed with subendocardial ultrasonic length transducers. A hydraulic vascular occluder was placed around the inferior vena cava (IVC) to sequentially alter preload. Dogs were allowed to recover from surgery 7-10 days and prior to experimentation, the autonomic nervous system (ANS) was blocked with propranolol (2 mg/kg), atropine methylnitrate (3 mg/kg) and hexamethonium (20 mg/kg) to prevent reflex changes in hemodynamics during changes in preload. Left ventricular and segment length data for loop generation were recorded in the conscious state and the IVC was then constricted to reduce left ventricular systolic pressure (LVSP) in 10 mmHg decrements. End expiratory pressure-length loops of 6 cardiac cycles were obtained at three decremental levels of LVSP. Anesthesia was induced with I or D on different days in each dog and maintained at 1.25 and 1.75 MAC. After 30 min equilibration, pressure length loops were obtained as described above. The anesthetic concentration was changed and measurements were repeated after similar equilibration. Changes between control and anesthetics were compared by ANOVA with repeated measures followed by Bonferroni's t-test ($p \leq 0.05$).



Linear relationships consistently resulted ($r^2 > 0.95$) when PRSW was plotted as a function of EDL in all groups. Increasing concentrations of D progressively decreased PRSW versus EDL slope consistent with a reduction in contractility. Concomitant decreases in +dP/dt, $+dP/dt_{50}$, and %SS were observed. Decreases in slope were also observed with I. Equianesthetic concentrations of D and I resulted in similar changes in PRSW versus EDL slope, +dP/dt, and dP/dt_{50} when these agents were directly compared.

The results indicate that D and I produce similar direct negative inotropic effects evaluated by PRSW versus EDL slope as an index of contractility in dogs with ANS blockade.

References:

1) Glower DD *et al. Circulation* 71:994-1009, 1985
2) Pagel PS *et al. Anesthesiology* (In press)

S208

TITLE: DROPERIDOL AND METOCLOPRAMIDE DO NOT PROVIDE EFFECTIVE ANTIEMETIC PROPHYLAXIS IN OUTPATIENT KNEE ARTHROSCOPIES

AUTHORS: SM Parnass, M.D., ER Corey, R.N., RJ McCarthy, Pharm.D., AD Ivankovich, M.D.
AFFILIATION: Dept. of Anesthesia; Rush-Presbyterian-St. Luke's Medical Center; Chicago, IL

Nausea and vomiting (NV) are disturbing side effects following outpatient anesthesia; the efficacy of prophylactic antiemetic treatment has been demonstrated for procedures at high risk for NV (i.e., laparoscopy) (1). Both droperidol (D) (2) and metoclopramide (M) (3) have been shown to be effective prophylactic premedicants in certain populations. The purpose of this study was to compare the efficacy of prophylactic intravenous D, M, and D/M in preventing postoperative NV for oupatient knee arthroscopies.

With HIC approval, 255 patients receiving general anesthesia for outpatient knee arthroscopies were prospectively studied: 35 patients (13.7%) received D .01 mg/kg and M 10 mg prophylactically during surgery; 47 patients (18.4%) received M 10 mg only; 45 patients (17.6%) received D .01 mg/kg only; and 128 patients (50.2%) rceived no prophylactic treatment. Demographic data was collected along with anesthetic agents and narcotics received, length of surgery and anesthesia, occurence of postoperative nausea and vomiting, and total time to discharge. Significance was assessed by χ^2 and analysis of variance at $p < 0.05$.

Age, weight, and gender were similar in all groups. All patients received a balanced anesthetic technique consisting of nitrous oxide/Isoflurane. 93% of patients received narcotics, while 7% received midazolam during surgery. Length of surgery was similar in all patients. No significant decrease in nausea or vomiting was seen in the groups that received D, M, or D/M postoperatively. Patients were treated with D .01 mg/kg following episodes of nausea or vomiting. Discharge times appeared to be slightly higher in the groups receiving antiemetic treatment.

In contrast to our previously reported findings for outpatient laparoscopy (1), the use of prophylactic antiemetics for knee arthroscopies is not efficacious and may be undesirable because of the potential for side effects and increased discharge time.

	ANTIEMETIC PROPHYLAXIS			
	D	M	D+M	Control
N	45	47	35	128
R/R N	14.0%	15.2%	17.1%	13.5%
R/R V	7.0%	6.5%	5.7%	10.3%
O/P N	24.4%	25.5%	34.3%	23.0%
O/P V	13.3%	19.1%	25.7%	12.7%
Total discharge time(min)	200±13.0	229±18.7	221±19.7	197±6.5

RR=recovery room;OP=outpatient;N=nausea;V=vomiting.

References:

1. Rothenberg DM. Anesthesiology 71:A322, 1989.
2. Vallanne J. Acta Anesthesiol Scand 29:359, 1985.
3. Diamond MJ. Can Anaesth Soc J 27:36, 1980.

S209

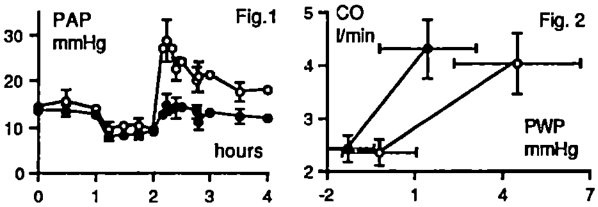
TITLE: MANAGEMENT OF INTRAOPERATIVE HYPOVOLEMIA IN SWINE USING 7.5% HYPERTONIC SODIUM CHLORIDE IN 6% DEXTRAN.

AUTHORS: J.M.S. Pascual, M.D., J.C. Watson, M.D., D.E. Runyon, B.S., C.E.Wade, Ph.D., and G.C. Kramer, Ph.D.
AFFILIATION: Letterman Army Institute of Research, Presidio of San Francisco, CA 94129

Introduction: Acute hypovolemia can be a life threatening event during anesthesia and surgery which requires prompt and efficient treatment. Conventional resuscitative measures include infusion of packed red cells and large volumes of isotonic crystalloid solutions. A 7.5% sodium chloride/ 6% Dextran 70 solution (HSD) has recently been advocated for pre-hospital treatment of hemorrhage, because of its effectiveness in small volumes. The use of HSD for correction of intraoperative hypovolemia has not been evaluated. Our purpose was to compare the administration of HSD and 0.9% NaCl (NS) to stabilize cardiovascular function following hemorrhage in anesthetized and surgically manipulated swine.

Methods: With the approval of the LAIR Animal Care Committee, 14 Yorkshire pigs (36±2 kg) were anesthetized with 1-2% isofluorane in 50% O_2/ 50% nitrous oxide. The animals were ventilated to maintain normal pCO_2 levels. Vascular cannulae were placed in the thoracic and abdominal aorta, and a thermodilution catheter was positioned in the pulmonary artery. A left thoracotomy was performed, for implantation of an electromagnetic flowmeter around the descending aorta. After one hr. of baseline, mean arterial pressure was reduced and maintained at 45 mmHg for one hr by hemorrhage. A continuous infusion of either NS or HSD was then started. Upon restoration of baseline levels of aortic blood flow (ABF) infusion rate was adjusted to maintain ABF stable for two hrs.

Results: Both regimens were able to restore baseline ABF and cardiac output within minutes. Arterial pressures and plasma volume expansion (Evans blue method) were similar in both groups. NS group required substantially higher infusion volumes (121±22 ml/kg) vs. HSD group (6.3±1.3 ml/kg). Total sodium load was actually higher with NS (15.5±1.7 mEq/kg) than with HSD (8.1±1.7 mEq/kg). NS treated animals exhibited significant increases in central venous and pulmonary artery pressures (Fig. 1), pulmonary vascular resistance, and right ventricular stroke work index. There was a leftward shift in the left ventricular preload/ cardiac output Starling relationship (Fig. 2) suggesting an increased contractile state after HSD treatment.



Figures: 1) Pulmonary artery pressure (PAP) in the NS group (o) and HSD group (●); 2) Cardiac output (CO) plotted vs. pulmonary wedge pressure (PWP), at end-hemorrhage (bottom) and 10 min post resuscitation (top).

Conclusion: There can be deleterious circulatory effects of conventional large volume resuscitation, including fluid and sodium accumulation, pulmonary hypertension, and right heart overload. HSD treated swine required significantly smaller infusion volumes to restore a normal hemodynamic profile, and had better cardiac performance, suggesting the superiority of HSD over isotonic fluid therapy for intraoperative hemorrhagic hypotension.

S210

TITLE: COMPARISON OF SUFENTANIL, FENTANYL, AND ISOFLURANE FOR NEUROANESTHESIA

AUTHORS: A.G. Pashayan, MD; B.L. Grundy, MD; M.E. Mahla, MD; B.D. Shah
AFFILIATIONS: Depts. of Anesth. and Neurosurg., Univ. of Fla. College of Med., Gainesville, FL 32610-0254

Introduction. In patients undergoing craniotomy, hypertension and respiratory depression should be avoided because they can increase intracranial pressure; also, a rapid emergence from anesthesia allows early neurologic assessment and, thus, treatment of surgical complications. We compared intraoperative stress response, emergence time, adequacy of spontaneous ventilation, and incidence of postoperative hypertension among sufentanil (SUF), fentanyl (FEN), and isoflurane (ISO).

Methods. After institutional approval and informed consent, 30 patients having craniotomy for aneurysm or tumor were randomized to 1 of 3 anesthetic regimens: SUF, 0.5 µg/kg at induction and 0.1 µg/kg/hr for maintenance; FEN, 5 µg/kg at induction and 1 µg/kg/hr for maintenance; or FEN, 2.5 µg/kg for induction, and ISO, 0.25-2%, for maintenance. Groups receiving SUF alone or FEN alone also received narcotics in a double-blind fashion and thiopental, 1-3 mg/kg/hr, during maintenance. All 3 groups received thiopental and vecuronium during induction and then vecuronium and vasodilators as needed. Intraoperative stress response (% min of vasodepressor infusion from the first dose of thiopental to discontinuation of N_2O, not including induced hypotension) and rapidity of emergence (min from discontinuation of N_2O to ability to open eyes on command) were recorded. Adequacy of spontaneous ventilation was assessed on a 4-point scale (see Table footnote). Incidence of vasodilator administration for 6 hr postoperatively was determined. Data were analyzed by ANOVA and Kruskal-Wallis test.

Results. Age, body mass index, body temperature 1 hr after operation, and duration of anesthesia/narcotic infusion were comparable among the groups. No study variable differed among the 3 groups (Table).

Discussion. We conclude that any of these three anesthetic techniques may be used effectively for craniotomy.

Acknowledgement. Supported by Janssen Pharmaceutica and Dept. of Veterans Affairs.

Table. Effects of Sufentanil, Fentanyl, or Isoflurane for Neuroanesthesia

	Sufentanil (n = 10)	Fentanyl (n = 9)	Isoflurane (n = 9)	P
Vasodilator infusion (% time)	34.2 ± 25.7	28.9 ± 26.7	24.4 ± 19.5	0.6803
Emergence time (min)	4.0 ± 2.9	3.0 ± 1.6	4.6 ± 2.4	0.1961
Ventilation score*				
1 hr	1.1 ± 0.4	1.4 ± 0.7	1.1 ± 0.3	0.6567
2 hr	1.1 ± 0.3	1.3 ± 0.5	1.0 ± 0.0	0.2871
3 hr	1.0 ± 0.0	1.4 ± 0.5	1.3 ± 0.5	0.1346
Postoperative hypertension (n of cases)	2	2	4	--

Values are mean ± SD except where noted.
*1-4 points: 1 is $PaCO_2 < 40$ mm Hg, 2 is 41-45 mm Hg, and 3 is > 46 mm Hg; 4 is use of mechanical ventilation or naloxone.

S211

THE RAPID RECOVERY OF RESPIRATORY FUNCTION AFTER LAPAROSCOPIC CHOLECYSTECTOMY

N. Patel, MD, C. Strogen, MD,
R. Kosinski, MD, C. Antiporda, MD,
G. Yuvorek, MD, and T. Baker, MS
Department of Anesthesiology, Monmouth Medical Center, Long Branch, NJ 07740

Introduction: Pulmonary function values are significantly reduced for 5-7 days after upper abdominal surgery (1), which includes subcostal incisions for cholecystectomy. This period of reduced respiratory function contributes to pulmonary complications. (2) The new laparoscopic cholecystectomy procedure avoids subcostal incision. This study investigated the effects of laparoscopic cholecystectomy on pulmonary functions.
Methods: Institutional Research Review Board approval and informed patient consent were secured with 41 ASA I and II patients being studied prospectively; 30 undergoing laparoscopic cholecystectomy and 11 open cholecystectomy by subcostal incision. All received narcotic and inhalation anesthesia, had preoperative bedside spirometery on the day of surgery and were followed at 6-12 hr and at 24 hr intervals until discharged. FVC, FEV, PEFR and 25-75%EFR were measured. Data were analyzed by ANOVA with $p \leq .05$.
Results: Both patient groups were similar in age, weight and duration of anesthesia. At 6-12 hr postoperatively, the respiratory functions of both groups were significantly depressed. At 24 hr postoperatively, the respiratory functions of the laparoscopic patients had recovered to 80% of control values and were significantly greater than those of the open cholecystectomy patients. Respiratory function recovery of the open cholecystectomy patients was slower, taking several days, and was similar to that reported elsewhere.(3) The average discharge time for the laparoscopic patients was 42.8 ±6.0 hr while it was 141.8±29.7 hr for the open cholecystectomy patients.
Discussion: Subcostal incision has been shown to contribute to pulmonary complications, and after subcostal incision, pulmonary function is significantly reduced for several days postoperatively.(1,3,4) The data from the present study clearly demonstrate that at 24 hr after laparoscopic cholecystectomy, pulmonary function has significantly recovered towards control values. The short hospital stay of the patients in this study indicate that the fast recovery of pulmonary function may contribute to decrease complications, early ambulation and quick hospital discharge.

References: 1. Am J Surg 128:376-382, 1974
2. Surg,Gyn Obstet 148:863-866, 1979
3. Am J Surg 122:621-632, 1971
4. Am Rev Respir Dis 112:541-583, 1975

S212

LOW PASS FILTERING OF ARTERIAL PRESSURE SIGNALS CAN IMPROVE ACCURACY: A STUDY BASED ON A CANINE MODEL

A. William Paulsen, MMSc(Anes), PhD
Baylor University Medical Center, Dallas, Texas

INTRODUCTION. Large discrepancies (50 to 60 mmHg) can exist between the actual arterial pressure at the site of measurement and the information displayed on the patient monitor. These errors are most severe in the systolic pressure, minimal in the diastolic pressure, and absent from the mean pressure. The magnitude of these dynamic errors is determined by the interaction between patient cardiovascular status (heart rate and myocardial contractility) and the resonant response characteristics of the tubing - transducer system. Various concepts have been implemented to minimize the resonant response of the monitoring system, from mechanical in-line damping devices to low pass electronic filtering within the monitor. Most monitor manufacturers include low pass filtering of pressure signals, but there is no universally accepted cutoff frequency for these filters, as they range from 6 Hz to 450 Hz. A cutoff frequency that is too high has no effect upon the resonant response of the monitoring system and is of no value. There is concern that a very low cutoff frequency, which would remove undesirable resonant characteristics, would remove important clinical information from the waveform. This study was undertaken to define the minimum acceptable low pass cutoff frequency that safeguards hemodynamic information while permitting response characteristics of the tubing - transducer system to be eliminated or minimized.
METHODS. Following approval of the Animal Care Committee, 3 unpremedicated mongrel dogs ranging from 14 to 29 Kg were anesthetized with iv thiopental (bolus induction, drip maintenance), intubated and mechanically ventilated. Millar PC-350 5 french catheter tip pressure transducers were inserted into the left ventricle and into the right femoral artery. These high fidelity pressure transducers were connected to wide bandwidth carrier amplifiers for an overall response of dc - 450 Hz and recorded on magnetic tape for off line analysis. The animals were subjected to extremes of cardiovascular function through the administration of isoproterenol, epinephrine, and propranolol plus 3% halothane. Data were analyzed using Fast Fourier Transform and polynomial regression techniques to determine frequency content of the pressure waveforms and the magnitude of the embedded noise. Systolic, diastolic and mean pressures were computed, as was the maximum dP/dt.
RESULTS. The worst case peripheral waveforms had pressures ranging from 56 to 213 mmHg systolic, 34 to 162 mmHg diastolic, means ranging from 43 to 182 mmHg, and maximum dP/dt ranging from 300 to 1998 mmHg/sec. Heart rate ranged from 136 to 273 beats/min. Left ventricular pressures ranged from 77 to 212 mmHg, 1.7 to 26 mmHg, 46 to 118 mmHg (syst, diast, mean), and maximum dP/dt from 626 to 6784 mmHg/sec. Measurement of systolic and diastolic pressure within 5 % in the periphery required 2 harmonics or a frequency response of dc to 6 hz for a maximum heart rate of 180 bpm. Left ventricular pressure required 5 harmonics or dc to 15 hz. Maximum dP/dt measured within 5% in the periphery required 20 harmonics or dc to 60 hz, and in the left ventricle 22 harmonics or dc to 66hz.
DISCUSSION. In view of large documented errors between clinically monitored systolic arterial pressure and return to flow cuff measurements in the same arm, some form of filtering would be beneficial to reduce measurement errors and the risk of potentially inappropriate therapy. In adults, 6 Hz low pass filters (pediatrics 8 hz) will substantially reduce errors in peripheral arteries without compromising accuracy of syst. or diast. values.

S213

Title: QUALITY ASSURANCE MONITORING AND EVALUATION IN A VETERANS AFFAIRS HOSPITAL: 30 MONTHS OF DATA

Authors: K.S. Pearson, M.D., F.L. Scamman, M.D.
Affiliation: Anesthesiology Service, VA Medical Center, Iowa City, IA 52246

Introduction: The Joint Commission has mandated that anesthesia services evaluate their quality of care on an ongoing basis.[1] We have monitored 64 indicators for 30 months and here present suggested criteria (acceptable rates of occurrence) and our rates for several of the indicators.

Methods: Following Institutional Review Board approval, on every anesthetic, a computer entry sheet, a list of the indicators and corresponding 3-letter codes which could be circled, was generated. The anesthetist circled the codes deemed appropriate. At the end of the procedure, a secretary entered the circled codes into a database (Informix SQL) running on a microcomputer (NCR Tower). A separate sheet was used for PACU and post-anesthesia data. Additional entries consisted of patient, staff, and resident identification data, date, room number, and times. Accuracy of entry was verified by a CRNA on each anesthetic.

Results: The table contains data abstracted from 4952 procedures performed since October, 1987: 3183 general, 1364 regional, and 405 MAC. The mean ASA status was 2.6 on elective and 3.3 on emergency procedures.

Discussion: Our data indicate, for 7 of the 10 monitors reported, that our rates are below criteria. Effective quality assurance efforts should improve patient care. QA monitoring must identify trends in care or single adverse clinical events that warrant further evaluation. This evaluation would then determine how to correct problems encountered.[1] Our clinical indicators are designed to provide early notification of any significant adverse trends, as well as to identify areas where improved clinical care would be possible. Our indicators and criteria serve the purposes set forth by the JCAHO.

References: 1. Monitoring and evaluation: anesthesia services. JCAHO, 1990. 2. Anesth Analg 67:843,1988. 3. Regional Anesthesia 12:159,1987. 4. JAMA 239:2566, 1978.

TABLE

INDICATOR	CRITERIA (%)	RATE (%)
OR Cardiac arrest	0^*	0.12#
Acute MI, OR to 24 hr	2^4	0.08#
Death, OR to 24 hr	0^*	0.24#
Failed spinal block	4^2	4.2
Failed axillary block	20^3	16.1
PACU stay > 2 hr	10^*	5.01#
Temp < 35.0 in OR	4^*	3.2@
Intubated > 8 hr postop	5^*	1.9@
Dangerous ECG rhythm	4^*	0.71#
Reintubation required	1^*	0.10@

* = Criteria determined locally by anesthesia staff
# - Based on all 4952 procedures
@ - Based on 3183 general anesthetics

S214

Title: PREMEDICATION IN PEDIATRIC OUTPATIENT SURGERY: COMPARISON OF ORAL MIDAZOLAM TO RECTAL METHOHEXITAL

Authors: M.A. Pilato, MD, E. Everts, MD, T. Yemen, MD, M. McManus, MD, R. Farrugia, CRNA, J. Gillis, CRNA, D. Greenblatt, MD,Ph.D.
Institution: Dept. of Anesthesia, The Children's Hospital, Harvard Medical School, Dept. of Clinical Pharmacology, Tufts-NEMC, Boston, MA

Introduction:

Several previous studies have shown that oral midazolam is an effective premedication in children having surgery.[1,2] These studies have not compared midazolam to currently used techniques of premedication; the optimum dose of midazolam is unknown. This randomized, blinded study compared three different doses of oral midazolam to rectal methohexital.

Methods:

After approval from the Human Research Committee, and after parental consent, the study patients were randomly assigned to one of four groups. These patients, ASA I or II, ages 1 to 6, underwent myringotomy and tube placement. Patients in Group 1 had oral midazolam 0.3 mg/kg mixed with 2 mls of a fruit flavored syrup. Group 2 had oral midazolam 0.5 mg/kg. Group 3 had oral midazolam 0.7 mg/kg. Group 4 received rectal methohexital 10%, 30 mg/kg. Patients were rated with a 5 point sedation scale: prior to medication, 10 minutes after medication, during induction and upon emergence from anesthesia. 10 minutes after medication, the patients had an inhalation induction with halothane and were maintained with halothane/N_2O/O_2. After anesthetic induction, patient blood was sampled for serum midazolam concentration. No narcotics were given during surgery or in the recovery room. The duration of the anesthetic was recorded. In the recovery room, the patients were observed in a blinded fashion and scored every 5 minutes for one-half hour. Time to discharge was recorded. Perioperative adverse reactions were noted. Sedation scores were analyzed using nonparametric data analysis. The Friedman statistic was used to analyze within groups and the Wilcoxon signed rank test was used to determine which groups were significantly different. The duration of anesthetic was analyzed by ANOVA. $P<0.05$ was considered significant.

Results:

No significant differences were found in age, weight or duration of anesthetic among the 4 groups. Significant changes in the level of sedation were found in all groups 10 minutes after the premedication was given. In Group 1, 84% separated from parents without problem and 66% of the patients tolerated mask induction. In Group 2, 90% separated from parents without problem and 75% of the patients tolerated induction. In Group 3, 88% separated from parents, 73% of the patients tolerated mask induction. In Group 4, 75% separated from parents and 75% tolerated induction. Time to discharge was not significantly different in any group. There were no adverse reactions from the study medications.

Discussion:

Oral midazolam was as effective as rectal methohexital for premedication and induction in pediatric outpatients. Separation from parents was easily accomplished 10 minutes after drug administration. Anesthetic induction was better tolerated in the 0.5 and 0.7 mg/kg dose range. There was no evidence of increased sedation in the midazolam groups as compared to the methohexital group.

---

[1] Anesthesiology, 69(3):A745, 1988
[2] Br J Anaesth, 61:390-396,1988

S215

TITLE: EFFECTS OF BELLOWS LEAKS ON ANESTHESIA VENTILATOR FUNCTION

AUTHORS: A. Podraza, M.D., M.R. Salem, M.D., T.L. Harris, H. Moritz, M.D.
AFFILIATION: Department of Anesthesiology, Illinois Masonic Medical Center, Chicago, IL 60657

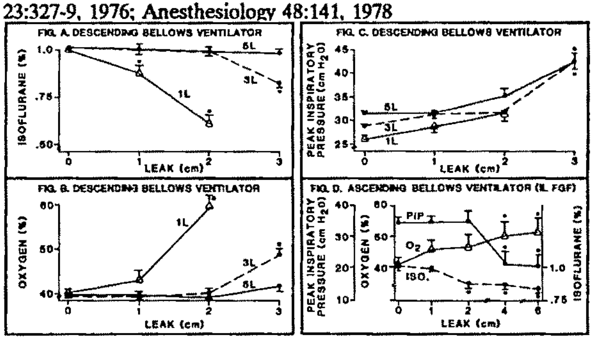
Introduction: Case reports have revealed intraoperative mishaps resulting from ventilator bellows tears.[1-3] These include increased tidal volume (V_t), hyperventilation, dilution of the inhalation anesthetic with driving gas (O_2), and awareness during anesthesia. The present controlled study was conducted to compare the effects of bellows leaks in two widely used anesthesia ventilators.

Methods: An Ohmeda 8000 anesthesia machine with a semi-closed circle absorber system was utilized for the study. Two types of ventilators were studied: the Ohio V5A (descending bellows ventilator) and the Narco Air Shields Ventimeter 1 (ascending bellows ventilator). A test lung was attached to the Y-piece of disposable EBA breathing tubes. The anesthesia machine was set to deliver 1% isoflurane in 60% N_2O/39% O_2 and the ventilator set to a V_t of 700 ml and a rate of 10 breaths/min. V_t and inspired gas concentrations were measured with a calibrated Wright respirometer and by mass spectrometry, respectively. Measurements of delivered concentrations of O_2, isoflurane and N_2O, V_t, and peak inspiratory pressure (PIP) were obtained with an intact bellows, and bellows with 1 through 6 cm leaks made by scalpel incision, after 10 minute equilibration periods. The measurements were obtained using 1, 3 and 5 L total fresh gas flow (FGF) rates. Five sets of data were collected for each experimental situation. Statistical analysis was performed using the Student's t-test and statistical significance accepted at $p < 0.05$.

Results: In the descending bellows ventilator, significant changes became evident at 3 cm leak, at all FGF rates tested and resulted in increased V_t, PIP, delivered O_2 and decreased delivered N_2O and isoflurane concentrations (Figs. A,B,C). At defects > 3 cm, the descending bellows ventilator ceased to cycle and hyperinflated the test lung. The ascending bellows ventilator performance remained normal except when low FGF (1L) was used in the presence of a large defect (> 4 cm). Under these conditions, a small but statistically significant increase in delivered O_2 and decreases in N_2O and PIP were seen. (Fig.D)

Conclusions: Tears in pneumatic ventilator bellows tend to increase V_t, PIP, and dilute inhalational anesthetics. The magnitude of change seems to be dependant on the type of ventilator, FGF, and the size of the leak. Higher FGF compensate for small (< 3 cm) leaks in both ascending and descending bellows ventilators. This study emphasizes the importance of careful inspection prior to use and periodic preventive maintenance of anesthesia ventilators.

References: Anaesthesia 34:178-9, 1979; Can Anaesth Soc J 23:327-9, 1976; Anesthesiology 48:141, 1978

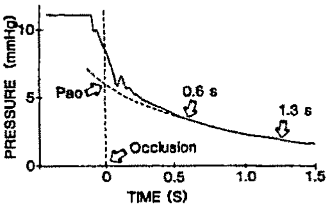


S216

Title: MEASUREMENT OF PULMONARY CAPILLARY PRESSURE FROM THE ARTERIAL OCCLUSION PRESSURE CURVE IN DOGS

Authors: R. G. Presson, Jr., M.D., S. C. Hillier, M.D., O. Okada, M.D., W. W. Wagner, Jr., Ph.D., T. S. Hakim, Ph.D.
Affiliation: Departments of Anesthesia and Physiology/Biophysics, Indiana University Medical School, Indianapolis, IN, and Department of Surgery, SUNY, Syracuse, NY

Measurement of pulmonary capillary pressure (Pcap) is superior to simple measurement of pulmonary wedge pressure in patients with lung injury because Pcap, not pulmonary venous pressure, primarily determines the rate of edema formation. Pcap has been estimated at the bedside by mathematical analysis of the pressure decay curve following pulmonary artery occlusion with a Swan Ganz catheter.[1] However, exact criteria for the analysis of this curve have not been established. This biphasic curve (fig) has an initial rapid pressure drop (thought to represent cessation of flow across arterial vessels) that is followed by a slow exponential decay (representing discharge of blood from the capillaries into the veins). When the slow phase is fitted to a monoexponential function and extrapolated back to the instant of occlusion, the arterial occlusion pressure (Pao) is obtained, a pressure close to the end of the arterial vessels and thus at the beginning of the capillary bed. The Pao most accurately reflects Pcap when the extrapolated data segment is limited to the time after which flow has stopped in arterioles but before capillary flow into venules decreases. To locate this data segment on the pressure decay curve, we performed the following experiment with the approval of our Animal Care Committee.



The left lower lobe was excised from 8 pentobarbital anesthetized dogs (19-29 kg), perfused with heparinized autologous blood at 37°C, and ventilated with $17\%O_2/6\%CO_2/77\%N_2$(pH=7.41 /PO_2=110/PCO_2=34). Venous pressure was held constant at 1 mmHg. Blood flow in the microcirculation of the lobe was observed through a microscope and recorded on videotape. Simultaneously, the arterial inflow tubing was rapidly occluded with a clamp containing a switch that marked the instant of occlusion, directed a computer to store the digitized pressure decay curve, and started a stopwatch (t=0) that was recorded on the videotape. Measurements were made during control, high flow, and arterial constriction (serotonin infusion). A time interval (0.6-1.3s, see fig) was determined from the videotape which under all conditions fell after the cessation of arteriolar flow but before capillary flow into venules slowed. Pao was obtained by extrapolation of this segment of the pressure curve back to the instant of occlusion. For comparison, the double occlusion pressure (Pdo), an accurate but clinically impractical measure of Pcap pressure, was also obtained by simultaneously occluding the arterial and venous lines.[2]

The results are shown in the table (values are $\bar{x} \pm SD$). Pao was not significantly different from Pdo (paired Student's t test).

	flow (ml/min)	Ppa* (mmHg)	Pao (mmHg)	Pdo (mmHg)
baseline	474±94	11.1±1.7	6.2±1.0	5.9±1.0
high flow	854±211	15.6±3.2	7.6±1.8	8.6±2.1
serotonin	472±136	18.2±3.9	8.5±3.0	9.2±2.3

*Ppa = pulmonary arterial pressure prior to occlusion.

The results suggest that extrapolation of the arterial occlusion pressure curve between 0.6 and 1.3 s back to the instant of occlusion could provide a close estimate of Pcap under a variety of clinical conditions.

1. Anesthesiology 66:614, 1987. 2. Ann NY Acad Sci 384:90, 1982.

S217

Title: CARDIOPLEGIC CONTRAST ECHOCARDIOGRAPHY IN PATIENTS WITH AORTIC REGURGITATION

Authors: T. Rafferty, M.D., and M. Durkin, M.B., F.C. Anaes.
Affilitation: Department of Anes. Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

Saline-contrast 2D echocardiography is a recognized diagnostic technique. The microcavitations associated with cardioplegia (CP) delivery can also serve as an echo-opaque medium.[1] The CP-contrast technique has not been applied to aortic regurgitation (AR). Further, left ventricular (LV) dimensional changes which result from AR-induced regurgitation of CP are not available. The following study applied the technique to delineate LV dimensional changes associated with aortic root CP administration in patients with clinically insignificant AR.

Method. Twelve adult coronary artery bypass graft patients (CABG) fulfilling Human Investigation Committee criteria were studied. Color flow Doppler (CFD) and 2D-echo recordings were obtained with a transesophageal (TE) 5.0 MHz phased-array imaging system. AR was mapped by CFD_{TE} prior to cardiopulmonary bypass (CPB). CPAR was studied by CP contrast 2D-echo. For LV diameter measurements (end-diastolic and asystolic, i.e. pre and post CP), the free wall was positioned close to the center of the field of view to maximize resolution. The CP solution was administered by roller pump via a 14 gauge cannula (driving pressures of 150-200 mmHg). Comparisons were by repeated measure analysis of variance.

Results. CPB was associated with decreases in LV diameter and LVOT area (P<.0001). The CP contrast technique allowed visualization of CPAR (Fig 1 arrow). CP microcavitations appeared within the LVOT in 12/12 cases, extended to the LV body in 11/12 cases, and to the left atrium in 10/12 cases. CP LV diameter and LVOT area exceeded CPB values (P<.0001). CP values exceeded pre-CPB values in 7/12 cases (Fig 2 closed circles). Clinical perception of LV distention prompted internal cardiac massage in 6/12 cases.

Conclusion. The CP contrast technique allowed 2D-echo visualization of CPAR. A standard technique of CP delivery was associated with LV dimension increases, which exceeded pre-CPB values in the majority of cases and required internal cardiac massage-LV decompression in instances. A clinical entity exists where the transvalvular pressure gradient associated with aortic root CP administration can cause CPAR-LV distention without the antecedant warning of "pump AI."

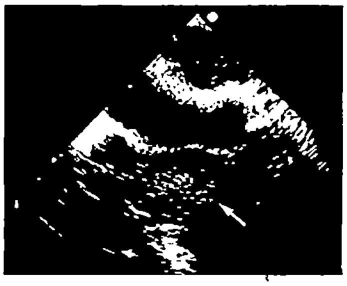


Fig. 1

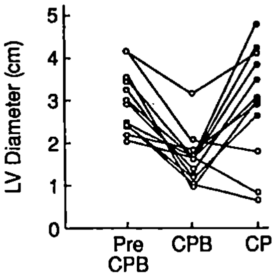


Fig. 2

References:
1. JACC 4:1029, 1984.

S218

Title: EFFECTS OF PERICARDECTOMY ON RIGHT VENTRICULAR DYNAMICS

Authors: T. Rafferty, M.D., M. Durkin, M.B., F.C. Anaes., R. Hines, M.D., J. Elefteriades, M.D., T. O'Connor, M.P.H.
Affiliation: Yale University School of Medicine, Yale-New Haven Hospital, Department of Anes. New Haven, CT 06510

Experimental evidence suggests that the pericardium exerts a restraining influence on the right ventricle (RV). This study coordinates echocardiographic and coincident RVEF thermodilution data under defined conditions of tricuspid valve integrity.

Methods. Fifteen adult coronary artery bypass graft patients were studied. Studies fulfilled Human Investigation Committee criteria. Hemodynamic measurements were obtained with a 50 msec response RV ejection fraction (RVEF) catheter. 2D-echo and color-flow Doppler (CFD) data were obtained with a transesophageal 5.0 MHz phased-array transducer. Long axis (LA) views transected the RV from base to apex with the mitral valve in the far field. In transgastric short axis (SA) views the RV was positioned close to the center of the field. Measurements included thermodilution RVEF, end-diastolic volume index (EDVI), LA and SA planed area excursion fraction ($RVEF\text{-}2D_{LA}$ and $\text{-}2D_{SA}$) and LA max major and minor axis shortening fractions. Patients with CFD or saline-contrast echo TR were excluded. Measurements were following induction (Fentanyl 115 ugm/kg)/intubation, sternotomy, and pericardectomy (P). Pearson correlation analysis determined relationships.

Results. The relationship between pre-P EDVI and the corresponding post-P changes was significant (r=0.83). RVEDP/change RVEDP (r=-0.67) and RVEF/change RVEF (r=-0.73) were also significant. Changes in EDVI were significantly related to changes in RVEF (r=-0.76). The $RVEF\text{-}2D_{LA}$/change $RVEF\text{-}2D_{LA}$ relationship was significant (r=-0.6). There was no significant difference between pre and post-P max major and minor $axis_{LA}$ shortening fraction relationships (r=0.6 vs 0.62). There was no relationship between pre-P $RVEF\text{-}2D_{SA}$ and changes in $RVEF\text{-}2D_{SA}$.

Conclusion. 1) The pericardium exerts a restraint on the RV, the response depending on volume status. Increased EDVI values decreased concomitant with increases in contractility indices with the converse for decreased values; 2) RVEDP changes were limited to decreases/minimal change, suggesting that they reflected intrapericardial and transmural pressure; 3) SA 2D-echo plane represented the inferior RV, and LA reflected a global image, exclusive of the outflow tract. Changes were confined to LA. There was no distinction between major and minor axis response to P, inferring that changes were in a plane superior to the apical segment and inferior to the max minor axis.

S219

TITLE ESTIMATION OF TRICUSPID REGURGITATION: COLOR-FLOW DOPPLER VERSUS SALINE-CONTRAST ECHOCARDIOGRAPHY

AUTHORS: T. Rafferty, MD, M. Durkin, MB, FC Anaesth, J. Mathew, MD, T. O'Connor, MPH

AFFILIATION: Department of Anesthesiology, Yale University School of Medicine, Yale-New Haven Hosp., New Haven, CT 06510

The prevalence of Doppler evidence of tricuspid regurgitation (TR) in normal subjects is between 33 and 50 %. Because of a paucity of data relating Doppler TR measurements to corresponding volume estimates, we compared color-flow Doppler (CFD) estimates of TR with simultaneously performed qualitative volume (saline contrast 2D-echo) determinations.

METHODS. Following Human Investigation Committee approval, standardized long axis tricuspid valve images were obtained in 20 adult CABG patients following induction/intubation, sternotomy, pericardiectomy, and before and after chest closure (n = 95) with a 5.0 MHz transesophageal phased-array transducer (TEE). CFD data were obtained at a focal depth of 12 cm with the transducer oriented to maximally demonstrate the regurgitant jet. TR was also assessed by the 2D-echo saline-contrast technique described by Lieppe et al.(1) Statistical analysis was by logistic regression with saline positive/negative TR as the dependent variable and continuous TR jet area as the independent variable.

RESULTS. 20/20 patients were successfully imaged. CFD TR jet area was significantly related to frequency of saline positive TR ($p<0.001$). Categorized CFD TR jet area and corresponding proportion saline positive TR are tabulated in Table 1. CFD sensitivity, specificity, and positive/negative predictive values of saline TR were 0.90, 0.52, and 0.45/0.92 respectively.

DISCUSSION. TR can be reliably imaged by the TEE CFD and saline-contrast 2D-echo. Our findings quantify the sensitivity, specificity, and predictive values of CFD with a qualitative volume estimate of TR. CFD was a highly sensitive indicator of saline-contrast defined TR, with a 90 percent sensitivity and a negative predictive value of 92 percent. However, the corresponding specificity and positive predictive values were relatively low, with only 26/58 positive CFD values being reflected in corresponding kinetic-volume estimates. This suggests that a large proportion of CFD defined TR is so trivial as to be undetectable by the volume standard, or, simply is a reflection of the right atrial c wave. It is recommended that the saline-contrast technique be routinely performed as a adjunct to CFD TR measurement.

Table 1	CFD TR JET AREA (cm^2)	PROPORTION SALINE POSITIVE
	0	0.08
	>0-0.6	0.24
	>0.6	0.94

Table 2	SALINE	CFD POSITIVE	NEGATIVE	TOTAL
	POSITIVE	26	3	29
	NEGATIVE	32	34	66
	TOTAL	58	37	95

REFERENCES.
1. Lieppe W, Behar V, Scallion R, Kisslo J. Circulation 57:128-132,1978

S220

TITLE : The Brain Laryngeal Mask Airway in Paediatric Anaesthesia

AUTHORS : A.Ravalia FFARCS, W.Fawcett FFARCS, P. Radford FFARCS.

AFFILIATION: QUEEN MARY'S HOSPITAL FOR CHILDREN, Carshalton, Surrey England.

INTRODUCTION: To assess the efficacy of the Brain Laryngeal Mask Airway (LMA) in Paediatric Anaesthetic Practice.(1,2)

METHOD: 200 consecutive paediatric cases presenting for general anaesthesia were looked at, provided there was no contraindication to the use of the LMA, i.e. a full stomach.

The three authors already had prior experience in the use of the LMA in paediatric and adult anaesthesia. Approval was obtained.

Premedication, induction and maintenance of anaesthesia were left to the discretion of the individual anaesthetist.

The following points were looked at :

1) ease of insertion
2) maintenance of clear airway
3) ability to assist ventilation.

RESULTS: In 78% of cases insertion of the LMA was successful at the first attempt, with good maintenance of the airway. With further manipulation or re-insertion of the LMA, a clear airway was achieved in 98% of cases. In only one case was it neccessary to replace the LMA with an endotracheal tube.

DISCUSSION: The LMA is now widely used in most hospitals in the UK. Adult(3) experience has already been reported. From our experience in general paediatric anaesthesia,we feel the LMA is a useful alternative to intubation of the trachea with all its attendant hazards and complications.

REFERENCES:
(1) The laryngeal mask-a new concept in airway management. Brit. J.Of Anaest. 1983,55:801
(2) Three cases of difficult intubation overcome by the LMA . Anaesthesia 1985,40: 353
(3) The laryngeal mask airway. A study of 100 patients during spontaneous breathing. Anaestesia 1989. 44: 238

S221

TITLE: INFLUENCE OF ANESTHETIC TECHNIQUE ON CEREBRAL BLOOD FLOW VELOCITY AUTOREGULATION DURING LOW FLOW CARDIOPULMONARY BYPASS

AUTHORS: D. Renz, G. Karliczek

AFFILIATION: Dept. of Anesthesia and Intensive Care, Kerckhoff-Klinik, 6350 Bad Nauheim/FRG

The following study was designed to investigate cerebral blood flow velocity (CBFV) autoregulation during pump flow reduction of the heart lung machine using balanced (Isoflurane/Alfentanil) or total intravenous (Methohexitone/Alfentanil) anesthesia.

After informed consent and with institutional approval CBFV of the middle cerebral artery was determined by transcranial Doppler technique (TC2-64B, EME) in 40 patients undergoing coronary artery bypass grafting. Anesthesia was induced and maintained with either Isoflurane/Alfentanil (n = 18) or Methohexitone/Alfentanil (n = 22). During CPB the Alfentanil infusion rate was 50 µg/kg/h supplemented with 0.25 MAC Isoflurane (group 1) or 1 mg/kg/h Methohexitone (group 2). During stable CPB (NPT 28 °C, alpha-stat $paCO_2$ 38 - 40 mmHg, Hct 24 Vol%) pump flow (Q) of the heart lung machine was reduced stepwise from 2.4 - 1.0 L/m^2/min to reduce non-coronary blood flow. Before and during Q reduction CBFV and MAP were measured continously in each patient of the groups. Data were analyzed using paired/unpaired t-test and linear regression technique.

The table shows the mean change of CBFV and MAP in response to a decrease in Q. NPT, $paCO_2$, Hct and demographic data were similar between groups. Q reduction of maximum 58 % from control (2.4 L/m^2/min) results in a corresponding CBFV reduction of only 28 % (group 1) resp. 24 % (group 2) despite a simultaneously reduced MAP to 54 % resp. 59 %. During Q reduction we found no significant differences of CBFV autoregulation between groups.

For a pump flow range of 1.4 - 2.4 L/m^2/min there was no significant correlation between CBFV and Q for group 1 (r = 0.150) as well as group 2 (r = 0.109).

Our results demonstrate a safe pump flow range of 1.4 - 2.4 L/m^2/min with preserved CBFV autoregulation without significant differences between Isoflurane or Methohexitone supplemented Alfentanil anesthesia.

		Q (L/m^2/min)						
		2.4	**2.0**	**1.8**	**1.6**	**1.4**	**1.2**	**1.0**
	Groups							
CBFV (cm/sec)	1	29	29	27*	26*	25*	23*	21*
		(11)	(10)	(10)	(8)	(8)	(7)	(7)
	2	26	25*	25*	24*	23*	21*	20*
		(9)	(8)	(8)	(8)	(7)	(6)	(5)
MAP (mmHg)	1	59	53*	49*	46*	41*	37*	32*
		(12)	(11)	(12)	(12)	(12)	(11)	(9)
	2	56	50*	47*	45*	41*	37*	33*
		(10)	(10)	(9)	(9)	(8)	(11)	(7)

Table 1: Results are mean (+ SD). Significant differences ($p < 0.05$) vs. control (Q = 2.4 L/m^2/min) within (*) groups. MAP: mean arterial pressure

---

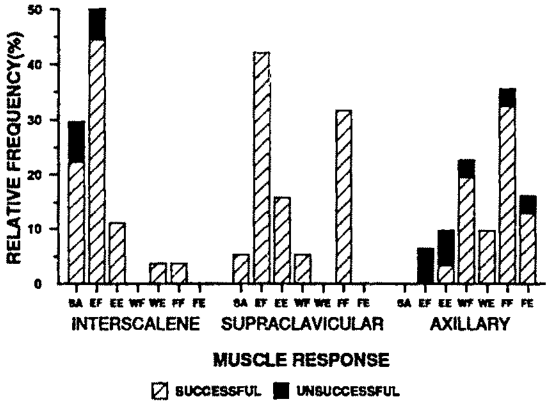
S222

TITLE: BRACHIAL PLEXUS NEUROSTIMULATION: MOTOR RESPONSE PATTERNS AT THREE SITES

AUTHORS: Francis X. Riegler, M.D.
AFFILIATION: Dept. of Anes. Univ of PA, Phila. PA

Introduction: Unique advantages of brachial plexus (BP) localization via neurostimulation (NS) include an objective endpoint and continuous feedback, since motor responses strengthen or weaken in proportion to needle tip distance from nervous tissue. The purpose of the present investigation is to determine differences in motor response patterns, minimum electrical currents, and success rates obtained with NS between interscalene (I), supraclavicular (S), and axillary (A) BP block.
Methods: With IRB approval, 77 ASA 1-3 patients, 13-75 yr, for upper extremity (UE) surgery, were prospectively studied. Localization via NS, site of approach (I, S, A), and local anesthetic agents were chosen by the attending anesthesiologist. Digistim III™ peripheral nerve stimulators were used. Ground pads were on the opposite shoulder, and insulated needles connected to the negative terminal. Initial stimulating currents were 3.0 mA. Needles were advanced to the position where UE muscle twitches were observable with the lowest stimulating current (nadir current). Success was defined as satisfactory analgesia and sensorimotor loss. Primary motor responses were shoulder abduction (SA), and flexion/extension of the elbow (EF, EE), wrist (WF, WE), or fingers (FF, FE). Presence or absence of secondary (lesser) responses, minimum stimulating currents, and success or failure were recorded.
Results: Primary motor responses for I (n=27) were clustered about the shoulder (30%) and elbow (63%), for S (n=19) about the elbow (58%) and fingers (32%), and for A (n=31) about the wrist (32%) and fingers (52%) (figure). Secondary responses occurred in 20% overall, 22% I, 11% S, and 23% A. Mean nadir current was identical for I, S, and A (0.7 ± 0.2 mA; range 0.2-1.5 mA). Success was 86% overall, 85% I, 100% S, and 77% A. For A, if elbow twitches were eliminated from analysis, success increased to 89%.

Discussion: Observed primary motor responses follow from the functional anatomy of the BP at each site. I is nearest cephalad roots, S nearest superior trunk, and A nearest terminal nerves. Heterogenous (primary plus secondary) responses are observed in approximately 1 of 5 cases. Mean nadir currents of 0.7 mA are readily obtainable at all 3 sites. Elbow twitches appear to be poor predictors of success at A, probably because radial triceps motor fibers and musculocutaneous biceps motor fibers lie outside the neurovascular sheath in the axilla. BP block with localization via NS yields a high rate of success for I, S, or A approaches.



S223

TITLE: CPB-ASSOCIATED PLATELET RECEPTOR LOSS CONTINUES INTO THE POST-BYPASS PERIOD.

AUTHORS: CS Rinder,M.D., HM Rinder,M.D., BR Smith,M.D.
AFFILIATION: Anes./Lab Med. Dept.,Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

INTRODUCTION: Cardiopulmonary bypass (CPB) produces multiple alterations in platelet structure and function, including decreases in the fibrinogen receptor, glycoprotein (GP)IIb/IIIa and the von Willebrand factor receptor, GPIb[1]. These changes, together with platelet activation and fibrinolysis, may contribute to the bleeding occurring after bypass. Using monoclonal antibodies (Mab) to these receptors measured by flow cytometry, we have followed patients after CPB to determine whether the receptor decreases found during CPB continue into the post-bypass period.

METHODS: Twelve patients undergoing surgery requiring CPB were studied after institutional review board approval. Samples of whole blood were drawn 5 minutes after heparinization, just prior to separation from CPB, and 1-4 hours after termination of CPB. Samples were fixed and labeled with red fluorescent Mab to one of the GP receptors and green fluorescent Mab to HLA-ABC. The samples were washed and bound Mab measured by flow cytometry. Density of the GP receptors was compared to the invariant membrane protein HLA-ABC based on the ratio of red to green fluorescence to allow detection of specific receptor loss as opposed to mechanical membrane fragmentation. Results were subjected to ANOVA analysis.

RESULTS: The density of both receptors decreased significantly by the end of CPB, and decreased further 1-4 hours after CPB to 32% of control for GPIb and 35% for GPIIb/IIIa. (Fig. 1) The decrease in GPIb after bypass correlated well with the time of drawing the last sample (r=0.8). GPIIb/IIIa did not show the same correlation (r=0.2), and neither sample correlated with duration of CPB.

DISCUSSION: Abnormal platelet function after CPB has been ascribed to causes temporally associated with CPB. These findings indicate that events leading to the loss of the fibrinogen receptor, GPIIb/IIIa, and the von Willebrand factor receptor, GPIb, continue into the early post-bypass period. In vitro work has demonstrated that plasmin cleaves both GPIIb/IIIa and GPIb from the platelet surface. We hypothesize that the fibrinolytic state created by CPB causes degradation of these receptors and continues into the post-bypass period, resulting in an ongoing platelet defect affecting both platelet adhesion and aggregation.

1. J. Clin. Invest. 78:340-8,1986.

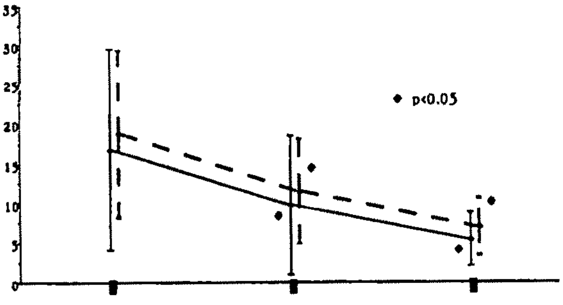


Figure 1: Ratio of GPIb/HLA ABC (——) and GPIIbIIIa/HLA ABC (- - -) at each of the above time points. Values are compared to the post-heparin value and analyzed by ANOVA.

S224

TITLE: COMPARISON OF THE EFFECT OF A SMALL BOLUS DOSE OF ESMOLOL AND LABETALOL ON THE HEMODYNAMIC RESPONSE TO ECT THERAPY.

AUTHORS: A.K. RISENMAY, B.S.N. AND M. NAKATSUKA, M.D.
AFFILIATION: MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA 23298

INTRODUCTION: Electroconvulsive therapy (ECT), widely used as a treatment for psychotic depression, is often accompanied by activation of the sympathetic nervous system. Transient hypertension and tachycardia caused by this sympathetic activation may be harmful to patients with cardiovascular disease. Therefore, we compared the effect of a small bolus dose of esmolol and labetalol on the hemodynamic response to ECT.

METHOD: After institutional review committee approval and informed consent, 10 patients undergoing a total of 23 ECT treatments were studied. All patient were monitored with a pulse oximeter, ECG, blood pressure by the Dinamap and cardiac output by thoracic electrical bioimpedance (TEB). ECT sessions were divided into 3 groups: (a) 7 cases pretreated with IV esmolol (0.5 mg/kg) 2 min. prior to ECT stimulus, (b) 8 cases pretreated with IV labetalol (0.2 mg/kg) 5 min. prior to ECT, and (c) 8 cases pretreated with IV saline. Each patient received two coded pretreatment injections in a double blind, randomized fashion. Anesthesia was induced with IV methohexital 50-80 mg and succinylcholine 50-80 mg. Heart rate (HR), systolic blood pressure (SBP), and cardiac output (CO) were recorded prior to ECT treatment, after induction of anesthesia, and every minute for 5 minutes after ECT treatment. Data were analyzed by a repeated measure analysis of covariance (ANCOVA), and $p<0.05$ was considered statistically significant.

RESULTS: Peak increase in HR, SBP, and CO occurred 2 minutes after ECT stimulus among the control group ($p<0.05$). Both esmolol 0.5 mg/kg and labetalol 0.2 mg/kg produced significant decreases in HR, SBP, and CO compared to the control group ($p<0.05$). Labetalol appeared to decrease SBP more significantly than esmolol.

DISCUSSION: Increases in HR, SBP, and CO following ECT can be detrimental to patients with ischemic heart disease or valvular disease. We demonstrated small doses of esmolol and labetalol can successfully modify hyperdynamic response to ECT. Labetalol may be more effective when ECT must be administered to a hypertensive patient.

1. MEAN CHANGES IN HR (beats/min)

	Ind.	1 min	2 min	3 min	4 min	5 min
Control	10	22	23	17	14	10
Esmolol	10	15	8	5	4	4
Labetalol	3	3	−1	0	−2	−3

2. MEAN CHANGES IN SBP (mm/Hg)

	Ind.	1 min	2 min	3 min	4 min	5 min
Control	5	18	29	25	17	10
Esmolol	−2	14	15	14	11	8
Labetalol	−7	−4	3	0	−3	−6

3. MEAN CHANGES IN CO (l/m)

	Ind.	1 min	2 min	3 min	4 min	5 min
Control	0.4	1.5	1.8	1.3	1.0	0.3
Esmolol	−0.3	0.6	0.6	0.4	0	0.2
Labetalol	−0.7	−0.2	0.1	−0.2	−0.2	−0.2

S225

TITLE: USE OF HIGH-DOSE MEPIVACAINE FOR AXILLARY BRACHIAL PLEXUS BLOCK

AUTHORS: Necita L. Roa, MD, Jane Exler, CRNA, Leroy V. Young, MD, Alex K. Mills, MD
AFFILIATION: Dept. of Anesthesiology and Surgery, Washington University Medical School, St. Louis, MO

Introduction Brachial plexus block is a common anesthetic technique for surgery of the upper extremity. A local anesthetic popular for this is mepivacaine. The commonly quoted maximum dose is 550 mg, which limits volume to less than 40 ml if a 1.5% concentration is used. We determined blood levels of mepivacaine following axillary block to determine if higher doses used for this block are a safe practice.

Methods This study was approved by the Institutional Review Board, and written informed consent was obtained from all participants. Subjects were healthy (ASA PS 1 or 2) adult patients scheduled for elective surgery. Patients were pre-medicated with midazolam (25 mcg/kg) and fentanyl (1-2 mcg/kg). The brachial plexus block was achieved using 10-11 mg/kg of mepivacaine (1.5% solution with bicarbonate added) injected using the trans-arterial technique ("single shot"). Arterial and venous blood samples were drawn at several points following injection.

Results A total of 9 patients were studied. In only one measurement did a level exceed 5 mcg/ml. Arterial levels rose more rapidly, and attained higher levels. Overall, arterial levels averaged 0.5±0.6 higher than venous levels for the time course studied.

Discussion Although levels were high (> 2 mcg/ml) even 3 hours after injection, these appeared to be receding. A few patients had levels drawn 4 hours post-injection, and these were low. Blood concentrations may have been affected by the fact that the axillary artery was punctured. Patients were discharged from recovery room in normal time course, and did not appear have any complications compared to patients receiving lower doses for their blocks.

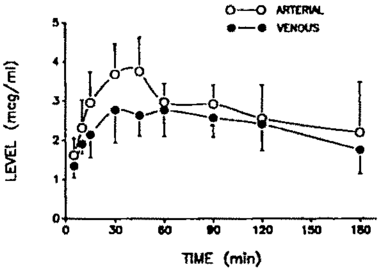
No patient demonstrated any signs of local anesthetic toxicity, although it could be argued that this might be masked by the benzodiazepine sedation.

Conclusion It appears that a dose of 10 mg/kg of mepivacaine for axillary brachial plexus anesthesia is safe in healthy patients.

References
1. Anesthesiology 37:277-287, 1972.
2. British Journal of Anaesthesia 37:394, 1965.
3. Anesthesiology 27:574-579, 1966.

time	arterial level	venous level
5	1.6 ± 0.7	1.3 ± 0.5
10	2.3 ± 0.8	1.9 ± 0.5
15	3.0 ± 0.9	2.1 ± 0.8
30	3.7 ± 0.9	2.8 ± 0.9
45	3.8 ± 0.9	2.6 ± 0.7
60	3.0 ± 0.7	2.8 ± 0.8
90	2.9 ± 0.7	2.6 ± 0.7
120	2.6 ± 0.9	2.4 ± 0.8
180	2.2 ± 1.1	1.8 ± 0.8

time in minutes, arterial and venous mepivacaine levels in mcg/ml ± s.d.



S226

Title: VARIATIONS IN IMPOSED WORK OF BREATHING WITH HEAT AND MOISTURE EXCHANGERS

Authors: W.D. Rodes II, MD; M.J. Banner, PhD; N. Gravenstein, MD
Affiliation: Depts. of Anesth., Neurosurg., and Physiol., Univ. of Fla., Gainesville, FL 32610-0254

Heat and moisture exchangers (HMEs), normally positioned between the endotracheal tube and the Y piece of the breathing circuit, increase resistance to spontaneous breathing[1]; this can increase work of breathing. We compared the work of breathing imposed (W) by HMEs under dry and saturated conditions.

A piston-driven, sinusoidal flow wave ventilator (Emerson) was modified to simulate spontaneous breathing; tidal volume (V_T) was set at 1 L, peak inspiratory flow rate at 30 L/min, frequency at 10 breaths/min, and inspiratory-to-expiratory ratio at 0.5. W was calculated by integrating the changes in pressure and V_T measured across 5 different kinds of HMEs (n = 3 each) (fig.). HMEs were first studied dry and then were subjected to saturated water vapor for 24 hr in a humidifed, ventilator breathing circuit. Data were analyzed by two-factor ANOVA and a Tukey multiple comparisons test with alpha set at 0.05.

W was significantly greater under the saturated condition than the dry with all HMEs. Under the dry condition, W was greatest with the Humid-Vent Mini and, under the saturated condition, with the Mallinckrodt, Siemens, and Humid-Vent Mini (fig.).

Normal total work of breathing in adults is 0.05 kg · meters/L of ventilation.[2] Dry HMEs imposed 20% to 60% additional work, while some saturated HMEs nearly double the total work of breathing. These data suggest that the increase in work imposed by an HME during spontaneous breathing increases over time as the device becomes saturated. Patients who cannot tolerate additional increase in work of breathing will benefit by having HMEs removed before spontaneous ventilation is initiated.

References
1. Am Rev Respir Dis 138:675, 1988.
2. Otis AB, in Handbook of Physiology. Section 3. Edited by Fenn WO, Rahn H. Washington, DC, Am Physiol Soc, 1964, pp 463-476.

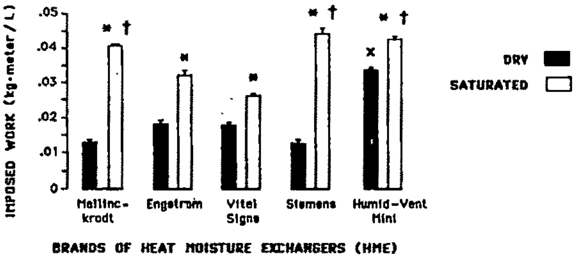


FIG. Imposed work of breathing with different kinds of heat and moisture exchangers. Data are mean ± SD. $\underline{P} < 0.05$ compared with *the same brand dry and other brands †saturated and ^{x}dry.

S227

TITLE: CAN THE NSAID NAPROXEN REDUCE POST-OPERATIVE PAIN IN LAPAROSCOPIC TUBAL LIGATION?

Authors: ME Rooney, BSP; WE Code, MD, FRCPC
Affiliation: Dept of Anaesthesia, Royal University Hospital, Saskatoon, Canada

INTRODUCTION: Postoperative pain and nausea are the most common causes of delayed discharge from gynecologic day surgery.[1] Previous investigations have assessed the efficacy of rectal administration of NSAIDS (non-steroidal anti-inflammatory drugs) preoperatively to reduce postopeative pain[2], but failed to control for perioperative narcotic use.

METHODS: In a randomized double-blinded manner, all ASA I and II patients scheduled for Day Surgery laparoscopic tubal ligation were considered for study. The study protocol was approved by our instituion's Human Experimentation Committee. Patients received either 275 mg or 550 mg naproxen or a placebo.

In order to standardize perioperative analgesia, no opiate premedicants were given, and fentanyl, 2 mcgs/kg was the only intraoperative narcotic used to supplement a pentothal, N_2O, isoflurane anaesthetic.

Patients marked a visual analogue pain scale preoperatively and at least twice following the procedure.

RESULTS: The Wilcoxon rank sum test was used for statistical comparison of the groups, with $p \leq 0.05$. There was no significant difference between study groups in terms of age, weight, or ASA status. 28 patients received placebo, 18 received 275 mg naproxen, and 7 received 550 mg naproxen.

In patients receiving 275 mg naproxen, there was a reduction in time to discharge (153.7 ± 55.2 min for drug vs 167.2 ± 56.1 min for placebo), but this difference was not significant. There was also no significant reduction in pain at either 1 or 2 hours postop with 275 mg naproxen when compared to placebo.

Treatment with 550 mg naproxen further reduced time spent in the day surgery unit (152.5 ± 36.2 min for drug vs 167.2 ± 56.1 for placebo), but was not statistically significant. However, despite small numbers this dosage did demonstrate a significant reduction in postop pain scores.

DISCUSSION: Our results show that 550 mg of naproxen given orally 1 hour preoperatively can reduce the amount of pain reported by patients undergoing laparoscopic tubal ligation. The naproxen effect appears to be dose related, and further study may confirm its ability to reduce postoperative stay as well.

REFERENCES: 1. Anesth Analg 1989; 68: 798-802.
2. Am J Obstet Gynecol 1985; 151: 175-77.

S228

TITLE: ARE ANESTHESIOLOGISTS PRACTICING PROPER INFECTION CONTROL PRECAUTIONS?

AUTHORS: AD Rosenberg, M.D., D Bernstein, B.A., ML Skovron, DrPH, S Ramanathan, M.D., H Turndorf, M.D.
AFFILIATION: Departments of Anesthesiology, Hospital for Joint Diseases Orthopaedic Institute and New York University Medical Center, New York, NY 10003

Introduction: The AIDS epidemic has heightened concern about the spread of infectious diseases in the healthcare workplace. The CDC[a] and ASA [b] have published guidelines for appropriate protection.[1] We randomly surveyed anesthesiologists (anes) to determine if they are protecting themselves and their pts from possible exposure.

Methods: A questionnaire (ques) was mailed to a random sample of 10% of ASA members (2544/25440). Four consecutive mailings with efforts to increase response rate (personalization of ques, handwritten message, and pre-paid reply mailer) were employed.[2] Questions included practice (prac) of wearing gloves, protective eyewear, recapping used needles, reusing common syringes (syr) or vasopressor (vasop) syr from pt to pt or changing needles before reusing syr, belief that blood can contaminate a needle placed in the injection (inj) port of an IV line and if the anes was vaccinated (vac) against hepatitis (hep). After 4 mailings, with a response of 41%, not including retirees or incorrect addresses (61 members), prac habits of 1015 anes toward themselves and their pts were determined. Comparisons were made (χ^2) to determine significance (sig) (at $p<0.05$ level) between responses of residents (res) vs. attendings (attend) and anes from NY, NJ, CT, and CA with others.

Results: The survey results are presented in Tables I and II. 58% (592/1015) claim they reuse syr from pt to pt. 33% (339) almost always change needles before reusing common syr. 37% reuse vasop syr from pt to pt. In addition, of the 76% who believe a needle becomes contaminated in the inj port of an IV, 54% (421/776) reuse a syr and 48% (333/776) reuse a vasop syr. There is a low incidence of glove or eyeglass use for protection, and a high rate of recapping of needles. Res have been vac against hep more frequently ($p<0.001$), reuse common syr less freq ($p<0.001$), reuse vasop syr less freq ($p<0.025$), and wear gloves more freq for starting an IV ($p<0.001$) or arterial line ($p<0.001$) than attendings. Those from NY, NJ, CT, and CA have been vac against hep more freq ($p<0.05$) recap needles less often ($p<0.05$), wear gloves for arterial line insertion more freq ($p<0.025$), but do not reuse syr or wear gloves for IVs at a sig different rate from others.

Discussion: The data suggest that anes do not use protective measures for themselves or their patients despite the knowledge that they work in a potentially infectious environment. There is a high frequency of syr and needle reuse from pt to pt despite the belief that needle contamination occurs. Needle recapping is common and hand or eye protection infrequent despite the high number of anes that have actively sought hep vac. Res are protecting themselves and their pts better than attend and anes from NY, NJ, CT, and CA follow more self-protection guidelines than others. Education must stress adherence to guidelines that will minimize exposure to both patients and anes.

TABLE I - ANESTHESIA PERSONNEL PRACTICE PT TO PT

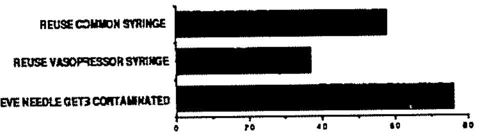
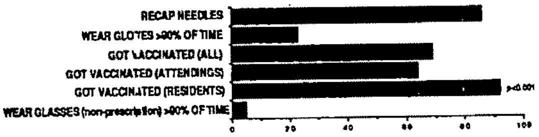


TABLE II - SELF PROTECTION OF ANESTHESIA PERSONNEL



a. Centers for Disease Control b. American Society of Anesthesiologists

1. Berry AJ: ASA Newsletter 53:4:8-9, 1989 2. AJPH 79:638-639, 1989

S229

TITLE: METOCLOPRAMIDE: AN ANALGESIC ADJUNCT TO PCA?

AUTHORS: W Rosenblatt, MD, L Saberski, MD, R Sinatra, MD, PhD, D Silverman, MD, A Cioffi, RN and L Preble, RN
AFFILIATION: Anes. Dept., Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

INTRODUCTION: Recent studies have demonstrated that the dopamine antagonist metoclopramide provides effective analgesia for renal colic (1) and improves analgesia when used for treatment of nausea during labor (2). Dopamine and its antagonists affect oviduct peristaltic motility (3). In light of analgesic potential of this agent in gynecologic procedures, we have evaluated whether administration of metoclopramide would reduce the pain associated with prostaglandin induced abortion in a randomized, placebo controlled, double blind trial in women (ASA II) electing mid-second trimester termination of pregnancy.

METHODS: Following Human Investigation Committee approval and informed written consent, 7 women received IV metoclopramide (10 mg) and 8 received saline, 10 minutes prior to initiation of Patient Controlled Analgesia (PCA) (morphine, 1mg with a 6 minute lockout, and 1mg/hr continuous infusion), approximately 2 hours after receiving intrauterine prostaglandin. Data included: Visual Analogue Scale (VAS) for pain (every 2 hours), PCA-morphine delivered, and time of fetal delivery. Data was analyzed by unpaired t-test, Wilcoxon signed ranked test, and 2-factor ANOVA for repeated measures, with $p<0.05$ considered significant.

RESULTS: There was no demographic or baseline VAS differences between groups. The metoclopramide group received less total morphine (mean 24.1 vs 52mg) ($p <0.02$), as well as less morphine on an every 2-hour basis (mean 3.1 vs 7.5mg/2hr) ($p<0.05$) during the first 10 hours of PCA. This group also had lower VAS scores at 2, 4 and 6 hours after PCA was begun ($P<0.05$). (table) and had earlier delivery of the fetus (mean 7.2 vs 15.3 hrs) ($p<0.05$).

DISCUSSION: We conclude that a single dose of metoclopramide reduces both the PCA-morphine requirements and VAS scores, and may facilitate passage of the fetus, in patients undergoing prostaglandin induced abortion. Our findings are consistent with the hypothesis that dysregulation of the smooth muscle in the oviduct and uterus may account for a significant amount of the discomfort encountered during this procedure, and that metoclopramide may provide a regulatory affect by reversing dopamine's inhibition of peristalsis, thereby reducing pain.

hour after	metoclopramide				placebo			
	VAS		MS		VAS		MS	
drug	median	range	mean(mg)	n	median	range	mean(mg)	n
2	3.5	(.5-5)	2.8	7	5.5	(1-7)	9	8
4	4	(.5-6)	3.2	7	5.5	(3-9.5)	7	8
6	3	(1-6.5)	3.3	4	6	(1.5-8)	6	6

1: Metoclopramide in the treatment of Ureterolithiasis. Uro Int 45:112-3, 1990
2: Comparison of the antiemetics metoclopramide and Promethazine in Labor. Brit Med J 290:1173-5, 1985
3: Is there a role for Dopamine in the Regulation of Motility of the Sow Oviducts? Pharmacological Research Communications 15(10):923-36, 1983

S230

Title: Ondansetron: A New, Effective Anti-Emetic Prevents Postoperative Nausea and Vomiting

Authors: F. Rosenblum, M.D., S.S. Azad, M.D., R. Bartkowski, M.D., J. Seltzer, M.D., J. Lessin, R.N., and A. Marr, CRNA
Affiliation: Jefferson Medical College, Thomas Jefferson University, Department of Anesthesiology, Philadelphia, PA 19107

Introduction: Ondansetron (Glaxo) is a carbazole derivative which acts as a serotonin type 3 receptor antagonist. It has been found to significantly reduce nausea and vomiting in patients receiving cisplatinum[1]. This study was designed to establish the efficacy of ondansetron administered to patients undergoing gynecologic operations with general anesthesia.

Methods: 50 ASA Class I and II women, ages 18 to 65, gave informed consent to participate in this IRB approved study. They were randomized in a double-blinded protocol to receive either ondansetron 8 mg IV or placebo IV over 2-5 min. The study drug was administered within 30 minutes before the operation and 8 hours later. All patients were premedicated with diazepam 5-10 mg p.o. Anesthesia was induced with thiopental 2-5 mg/kg, dTC 3-6 mg and succinylcholine 1-1.5 mg/kg. Following intubation, anesthesia was maintained with 70% N_2O:30% O_2, isoflurane and fentanyl. Neuromuscular blockade was established with pancuronium, atracurium or vecuronium and reversed with neostigmine and glycopyrrolate.

An emetic episode was defined as a single episode of vomiting or retching followed by an asymptomatic period of at least one minute. The total number of emetic episodes were recorded. Nausea scores O (no nausea) to 10 (severe nausea) were elicited upon arrival in the recovery room, at 30 minute intervals for 2 hours, at 1 hour intervals for 8 hours and 24 hours after the initial dose. Statistical analysis was done by Mann Whitney U test for intergroup comparisons and ANOVA for repeated measures for nausea scores. $P < 0.05$ was significant.

Results: The ondansetron group experienced significantly fewer episodes of emesis than the control group (Figure 1). A significant benefit was also found for the ondansetron group when analyzed for the incidence of either emesis or withdrawal from the study to receive a rescue drug. Those subjects who required a rescue drug were not significantly less in the ondansetron group. Nausea scores were significantly lower during the 24 postoperative hours for patients receiving ondansetron (Figure 2).

Figure 1

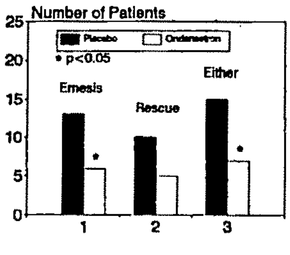
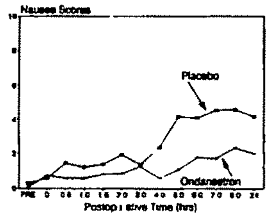


Figure 2



Discussion: Ondansetron has been found to be a safe effective agent to reduce nausea and vomiting in postoperative patients

Reference:

1. Cubeddu LX, Hoffman IS, Fuenmayor NT, Finn AL: NEJM 1990;332:810-815.

S231

Title: Evaluation of a 32 gauge catheter for continuous
spinal anesthesia during lithotripsy

Authors: G.W. Rung, M.D., S.K. Clark, M.D.,
J. R. Mostrom, M.D., S. Riemondy, R.N.,B.S.N.
Affiliation: Anesthesia Department, Pennsylvania State
University College of Medicine, Hershey, PA 17033

Introduction: Extracorporeal shockwave lithotripsy (ESWL) is a technique which breaks renal calculi into small fragments that may be passed spontaneously. The procedure requires anesthesia to prevent discomfort from the shockwave.[1] We favor regional anesthesia because awake patients may cooperate with positioning, report difficulties, and the problems associated with general anesthesia are avoided. Continuous lumbar epidural anesthesia has been used in 97% of our patients in the past with success. Theoretically, a continuous spinal technique would provide a denser block with faster onset using only a fraction of the dose required by an epidural anesthetic.[2] However, the increased risk of postdural puncture headache (PDPH) associated with spinal (versus epidural) anesthesia has curtailed the use of continuous spinal anesthesia in the past.[3] We evaluated the effect of a newly developed[4] 32 gauge spinal catheter on the incidence of PDPH and other clinical parameters, compared with 20 gauge spinal and epidural catheters.

Methods: After institutional review board approval and informed consent, we plan to study 60 adult patients scheduled for elective ESWL. The patients are randomly assigned to one of three study groups: Group 1 will receive an epidural anesthetic using a 20 gauge catheter; Group 2 will receive a spinal anesthetic using a 20 gauge catheter; and Group 3 will receive a spinal anesthetic using a 32 gauge catheter. Lidocaine will be used as the local anesthetic for all groups. The following parameters will be measured in each patient: time required for catheter insertion, time required to obtain T4 sensory level, lidocaine dose, incidence of >20% decrease in systolic blood pressure, incidence of patient discomfort during lithotripsy, duration of lithotripsy, time until bilateral toe movement, and incidence of PDPH.

Results: To date, 27 patients have been studied. The three experimental groups are well matched for age, sex, height, weight, and ASA physical status. All epidural catheters were successfully inserted. Of the spinal catheters, one of the 20 gauge and 5 of the 32 gauge catheters could not be inserted. Individual results are shown in the table.

Conclusions: Initial difficulty with insertion of the 32 gauge catheter resulted in the low success rate for that group, but improved with experience. The shorter preparation time and lower lidocaine dose required by the spinal technique warrant further study. A greater number of patients and more experience with the catheters are required before a final evaluation of the technique can be made.

Table. Individual patient results (mean ± SEM)

	Epidural 20G N=9	Spinal 20G N=9	Spinal 32G N=9
Successful	9 (100%)	8 (89%)	4 (44%)
Insert time (min)	5.5 ± 1.3	9.7 ± 2.6	10.1 ± 2.3
T4 level (min)	19.7 ± 2.0	8.6 ± 3.1 *	20.0 ± 6.7
Lidocaine dose (mg)	666.7 ± 66.7	228.1 ± 26.1**	181.3±27.7**
> 20% decrease BP (#)	3 (33%)	5 (56%)	2 (22%)
Discomfort (#)	1 (11%)	0	0
ESWL time (min)	37.8 ± 6.5	44.0 ± 4.8	38.3 ± 17.4
Toe movement (min)	42.9 ± 14.0	79.4 ± 8.3	89.3 ± 12.3
PDPH (#)	0	2 (22%)	0

(versus epidural 20G): * p= 0.008 **p< 0.001

References: 1. Abbott MA, Samuel JR, and Webb DR: Anaesthesia 40:1065-72, 1985 2. Peterson DO, Borup JL, Chestnut JS: Reg Anesth 8:109-113, 1983 3. Vandam LD, Dripps RD: JAMA 161:586-591, 1956 4. Hurley RJ, Lambert DH: Anesth Analg 70:97-102, 1990

S232

Title : SPINAL AND INTERPLEURAL
BUPIVACAINE FOR PERCUTANEOUS
NEPHROLITHOTOMY.

Autnors: MMA Saied, M.D., ZM Sonbul,
M.D., M El-Kenawy, M.D. and
MM Atallah, M.D.
Affiliation:Urology & Nephrology Center
Mansoura University,
Mansoura-Egypt.

Introduction: The promising interpleural block (IPB) stimulated the comparison of its adjuvant effect to spinal analgesia for percutaneous nephrolithotomy (PCNL) with that of meperidine-diazepam.

Materials and Methods:- The protocol was approved by the responsible authority, and special informed consent was secured from all patients subjected to IPB. 25 patients received spinal analgesia 15 mg 0.5% heavy bupivacaine for PCNL were randomly allocated to receive the adjuvant effect of either meperidine 1mg/kg iv and diazepam 10mg total dose (n=10), or IPB with 10ml 0.5% plain bupivacaine (n=15). Perioperative pain was assessed using prince Henry scale (1).

Results:- IPB produced pain free operative procedure, and the patients needed less frequent administration in the postoperative period. Meperidine-diazepam resulted in pain free operative interference in 20% of patients, and they needed more frequent postoperative meperidine (1mg/kg im) administration.

Discussion:- IPB is a simple technique that can be used as adjuvant to spinal analgesia during the perioperative period in patients subjected to PCNL.

References:- (1) Stromskag KE, Reiestad F, Holmqvist ELO, Ogenstad S. Intrapleural administration of 0.25%, 0.375%, and 0.5% bupivacaine with epinephrine after cholecystectomy. Anesth. Analg. 1988; 67: 430-434.

S233

TITLE: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF TRANSDERMAL FENTANYL FOR POST-HYSTERECTOMY ANALGESIA

AUTHORS: AN SANDLER MB, AD BAXTER MB, P NORMAN MD B. SAMSON MD, S LAWSON RN, K HULL RN.

AFFILIATION: DEPTS. OF ANESTHESIA, TORONTO GENERAL HOSPITAL AND OTTAWA GENERAL HOSPITAL, ONTARIO, CANADA

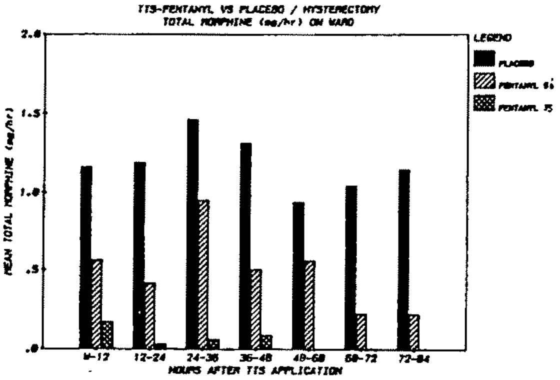
Recent incorporation of fentanyl into a Transdermal Therapeutic System (TTS) has provided continuous postoperative analgesia after several surgical procedures. This study evaluated the use of TTS-fentanyl for post-hysterectomy analgesia.

Methods: With institutional approval and informed consent, 10 patients rated ASA 1-2 undergoing abdominal hysterectomy were entered into a randomized, double-blind, placebo-controlled trial comparing two dosage levels of TTS-fentanyl. Group I (placebo, N=4) were treated with non-opioid TTS patches. Group II (N=3) were treated with a TTS-fentanyl 50 patch (releases 50 ug/hr fentanyl) and Group III (N=3) with a TTS-fentanyl 75 patch (releases 75 ug/hr fentanyl). Blinding was achieved by applying the two different sized patches (active or placebo) to all patients, thus allowing the required placebo/fentanyl combinations. TTS patches were applied two hr preop after a diazepam premedication. Patients were given a standard general anesthetic including sufentanil 0.5 ug/kg, thiopental 3-5 mg/kg, pancuronium 0.05-0.1 mg/kg, N_2O and isoflurane. Postoperatively, all patients used a morphine-loaded PCA device as required for supplementary analgesia. Patients were monitored continuously by trained nursing personnel for 72 hr after the application of the TTS-patches, and for 12 hr following removal of the patches. Analgesia was assessed by visual analogue score (VAS 0=no pain, 10=maximum pain) and PCA morphine requirement. Respiratory effects were monitored continuously with Respiratory Inductive Plethysmography (RIP) and pulse oximetry. Results were analyzed using ANOVA.

Results: There were no significant differences between groups for age, weight, height, or duration of surgery. Gps II and III used less morphine (p=0.059) than Gp I (placebo). All groups achieved satisfactory analgesia (VAS<3) although VAS scores in Gp III were lower than in Gp I. Respiratory events (decreased respiratory rate, apnea, desaturation) were minimal and of no clinical significance for any of the patients. This pilot study has suggested the analgesic effectiveness and respiratory safety of TTS-fentanyl 50 and 75 patches for lower abdominal surgery. Further large scale studies are currently underway.

TABLE 1 GROUP MEANS ± SD

	GROUP I	GROUP II	GROUP III
morphine in PARR (mg/hr)	11.08±1.37	13.52±2.18	7.67±5.72
morphine on ward (mg/hr)	1.18±0.36	0.48±0.23	0.04±0.03
VAS score	51.1±21.9	39.5±24.1	12.3±4.5



S234

Title: CALCIUM DEPENDENT INHIBITION OF SYMPATHETIC GANGLIONIC TRANSMISSION BY ISOFLURANE IN THE DOG

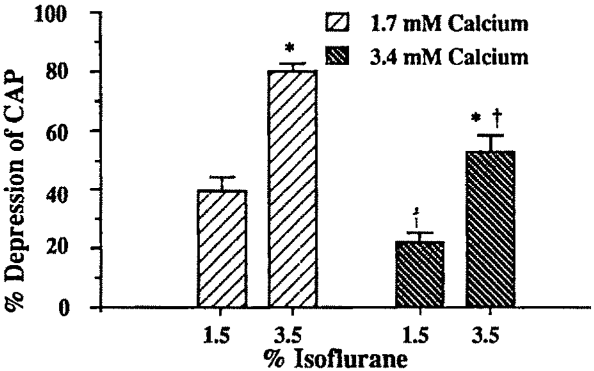
Authors: Schedewie HK MD PhD, N Boban MD, JP Kampine MD PhD and ZJ Bosnjak PhD

Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

Isoflurane (ISO) has been shown to impair synaptic transmission at the canine stellate ganglion (SG),[1] but the mechanism of this action remains to be elucidated. Since ISO is a known inhibitor of inward calcium (Ca^{++}) current at the myocardium,[2] the purpose of this study was to investigate whether ISO may have a similar effect at the SG. Therefore, we examined the depressant effect of ISO on the evoked compound action potentials (CAP) recorded in vitro at different Ca^{++} concentrations.

After institutional approval, 15 SG were isolated from adult mongrel dogs after thiopental anesthesia, desheathed and superfused with standard Krebs solution (Ca^{++} 1.7 mM) at 37°C, pH 7.4, O_2 97% and CO_2 3%. The preganglionic T3-ramus and postganglionic ventral ansa subclaviae were placed on bipolar tungsten electrodes for stimulating and recording purposes, respectively. CAP measurements were done under conditions of supramaximal stimulation at 0.4 Hz. CAP depressions resulting from 1 and 2 MAC (1.5 and 3.5%) of ISO were compared to bath Ca^{++} concentration of 1.7 and 3.4 mM. Control measurements of CAP were performed after each ISO exposure, and the controls were averaged. ISO vaporizer settings of 1.5 and 3.5%, yielded average vapor concentrations by MS of 1.1 and 2.45%, and bath concentrations by GLC of 0.5 and 1.17mM, respectively. The paired t-test was used for statistical analysis.

ISO caused a dose-dependent CAP depression which was readily reversible. This effect was antagonized by higher bath Ca^{++} concentrations. At a bath Ca^{++} concentration of 1.7 mM, mean (±SE) CAP depression was 39±5 and 80±3 percent, for ISO concentrations of 1.5 and 3.5%, respectively. By contrast, at a bath Ca^{++} concentration of 3.4 mM, CAP depression was only 22±3 and 53±6 percent, respectively (Figure). Since higher concentrations of extracellular calcium effectively antagonized depression of ganglionic transmission, it is likely that ISO action involves the inhibition of Ca^{++} influx at the SG presynaptic terminals.



* $p<0.01$ vs 1.5% ISO
† $p<0.01$ vs 1.7 mM Calcium

References: 1) Anesthesiology Abstracts 1990 (in press);
2) Anesthesiology 69(3A): A425; 1988

S235

Title: PENTASTARCH DECREASES BLOOD-BRAIN BARRIER PERMEABILITY FOLLOWING TEMPORARY CEREBRAL ISCHEMIA IN RATS

Authors: RM Schell MD, DJ Cole MD, TN Osborne AHT
Affiliation: Department of Anesthesiology, Loma Linda University, Loma Linda, CA.

Introduction: A consequence of focal cerebral ischemia is injury to the blood-brain barrier (BBB), which dependent on the severity of the insult permits entry of serum proteins into the brain and secondary injury.[1] Previous studies in other organ systems report that microvascular permeability is reduced when specific macromolecular weight fractions (100-300,000 daltons) of hydroxyethyl starch are given.[2] We evaluated the affect of pentastarch (≈264,000 daltons) on BBB permeability after middle cerebral artery occlusion (MCAo) in isoflurane anesthetized (1.2 MAC) rats.

Methods: Approval was obtained from the institutional Animal Care Committee. Male rats were subjected to 180 min of MCAo, followed by 30 min of reperfusion. Glucose, pH, $PaCO_2$, PaO_2, temperature, and hematocrit were monitored. After 120 min of MCAo, the animals were given one of the following: **10% Pentastarch** (n=5)-10 $ml\cdot kg^{-1}$ bolus, and a 10 $ml\cdot kg^{-1}hr^{-1}$ infusion, or **10% Albumin** (n=5)-a comparable dose of 10% albumin. Evans Blue (30 $mg\cdot kg^{-1}$ [EB]) was given, the brains were harvested, and the concentration of EB determined by spectrophotometric assay (EB is an indicator of vasogenic edema). The data were compared by a mean t-test.

Results: There was no between groups difference in the physiologic data. Evans Blue was less in the Pentastarch vs Albumin group ($p < 0.05$, see Table 1).

Discussion: In the early period of reperfusion there is an acute opening of the BBB, with abnormal entry of serum protein into the brain and vasogenic edema.[3] Our study supports the hypothesis that macromolecules in the 100-300,000 dalton range reduce pathologic increases in microvascular permeability during this period.[2,4] The proposed mechanism whereby these macromolecules reduce microvascular permeability is via a molecular sealant effect at separated endothelial gap junctions.[2,4]

Group	Evans Blue
Pentastarch	6.1±2.3
Albumin	15.3±6.3*

Table 1-Evans Blue ($\mu g\cdot g^{-1}$ of tissue, mean±SD) in the ischemic hemisphere. *$p < 0.05$ vs the Pentastarch group.

References:

1. *Br J Anaesth* 57:18-22, 1985.
2. *Surgery* 105:625-631, 1989.
3. *Acta Neuropathol* 68:122-129.
4. *Crit Care Med* 17:1306-9,1989.

S236

Title: INTRAOPERATIVE CATECHOLAMINE, RENIN AND HEMODYNAMIC RESPONSES FOLLOWING PROPHYLACTIC ADMINISTRATION OF INTRAVENOUS ENALAPRILAT

Authors: H Schieren, PhD, M Heropoulos, MD, JL Seltzer, MD, RR Bartkowski, MD, PhD, MC Torjman, MEd, J Lessin, RN, C Moody, BA, ME Goldberg MD
Affiliation: Department of Anesthesiology, Jefferson Medical College, Philadelphia, PA 19107

Introduction: Oral enalapril and intravenous enalaprilat have been reported to improve perioperative cardiovascular stability[1,2]. Adrenergic stimulation, as well as activation of the renin-angiotensin system (RAS), may be associated with the hemodynamic instability which occurs during surgical stress in man[1,3]. Therefore, we evaluated intraoperative hormonal and hemodynamic parameters in patients pretreated with the intravenous angiotensin-converting enzyme inhibitor, enalaprilat.

Methods: After IRB approval and informed consent, 10 ASA I-II patients scheduled to undergo limb surgery, ages 18-75, were randomized to receive enalaprilat (1.25 mg) or placebo intravenously 20 minutes prior to intubation. All patients received the same anesthetic regimen. Plasma catecholamines were measured by HPLC with electrochemical detection. Plasma renin activity (PRA) was determined by RIA. Blood pressure and heart rate were recorded using an automated blood pressure cuff. Statistical analyses were performed by ANOVA with repeated measures; $p < 0.05$ was considered to be significant.

Results: Norepinephrine and epinephrine levels were not significantly different between enalaprilat and placebo groups (Figure 1). PRA was significantly higher in the enalaprilat group than in the placebo group at post-intubation, post-incision and end-surgery (Figure 2). Both MAP ($p < 0.005$) and heart rate ($p < 0.005$) were significantly elevated post-intubation in the placebo group.

Discussion: Interestingly, catecholamine levels, hence sympathoadrenal activity, did not increase significantly as did MAP and heart rate after intubation in the placebo group. However, PRA was significantly elevated in the enalaprilat group indicating activation of the RAS, albeit amplified due to the loss of biofeedback inhibition. These results suggest that the RAS may play a larger role than heretofore expected in the mediation of intraoperative hypertensive events, events controlled by enalaprilat.

Figure 1

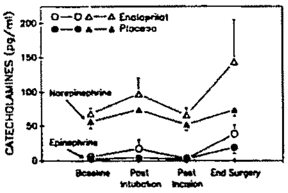
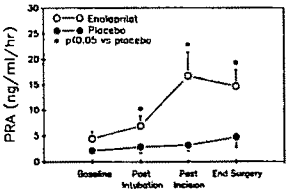


Figure 2



References

1. Anesthesia 43:935-938, 1988.
2. Anesth Analg 69:833-839, 1989.
3. J Clin Endocrinol Metab 45:936-944, 1977.

S237

Title: **DO LOCATION AND SIZE OF BRAIN TUMOR AFFECT EMERGENCE FROM ANESTHESIA?**

Authors: A. Schubert, M.D.; E. Bloomfield, M.D.; J.R. Little, M.D.; Z.Y. Ebrahim, M.D.; M. Grimes-Rice, BSN; L Paranandi, MSHP
Affiliation: Cleveland Clinic Foundation, Cleveland, OH

Introduction: Although delayed emergence from anesthesia after craniotomy is recognized anecdotally[1], little published information exists regarding its incidence and predisposing conditions. Knowledge of emergence characteristics after intracranial neurosurgery could provide useful information to the anesthesiologist when planning the anesthetic regimen and postoperative ventilatory care. In the present study, patients undergoing brain tumor resection were prospectively evaluated and compared to patients undergoing decompressive spine surgery.

Methods: With institutional approval and informed consent, 38 patients (craniotomy: n=27, spine surgery n=11) were prospectively studied. Each unpremedicated patient was anesthetized with thiopental 2-3 mg kg^{-1}, sufentanil 1-1.5 μg kg^{-1} followed by an infusion at 0.2-0.5 μg.kg.$^{-1}$; N2O, isoflurane (iso, ≤0.5%) and relaxant. Sufentanil was discontinued one hour prior to the end of surgery. No other anesthetics, sedatives, antiemetics or atropine were administered. PCO_2 was controlled to 27±3 mmHg endtidal (ET) and blood pressure was kept within 20% of preoperative values. Mental status was assessed at 15-minute intervals after discontinuance of N_2O for 1 hour and hourly thereafter for 4 hours. Lesion size, mass effect and location was recorded. Lesions were considered large if their diameter exceeded 30 mm and were associated with mass effect. Groups were compared with the two-sample t-test or the Wilcoxon rank sum test.

Results. The craniotomy group was similar to control with respect to sex, height, duration of surgery, sufentanil dose, emergence temperature, time of discontinuance of sufentanil, iso and N_2O. Craniotomy patients were somewhat younger (49±13 vs. 56±18 yrs.) and weighed less (73±13 vs. 93±18 kg). In the craniotomy group, 55% of tumors were supratentorial and 63% large. Median times from discontinuance of N_2O to various emergence milestones appear in Table 1. Although no significant difference was detectable statistically within the craniotomy group, patients with emergence times > 1 hour almost always had large supratentorial lesions.

Discussion. Our preliminary results indicate that anesthetic emergence after craniotomy for tumor is significantly longer than after non-cranial procedures. Lesion size and location above or below the tentorium did not appear to influence emergence times. However, the as yet small sample size may obscure a trend toward longer emergence in larger lesions located in strategic areas. Further study investigating other factors such as frontal lobe retraction may provide additional insight.

Reference: Med J. Aust 2:366-371, 1973.

Table 1 **MEDIAN EMERGENCE TIMES (Minutes)**

	Control [n=11]	Tumor [n=27]	Large [n=17]	Small [n=8]	Supra [n=14]	Infra [n=11]
Eyes Open	3	4.5	4.5	4	5	2.5
Extubation	6	5	5	5	6	3.5
Moves on Command	0	0	0	0	0	0
Orient/Time	0	15*	15	15	15	22.5
Orient/Place	0	15*	15	15	15	15
Orient/Person	0	15*	15	15	15	15

*$p<0.05$ vs. control

S238

Title: **MOCK ORAL EXAMINATIONS RESULTS ARE UNRELATED TO DAILY FACULTY EVALUATIONS**

Authors: A. Schubert, M.D.; Frances M. Rhoton, Ph.D.; Shelly Sords, M.B.A.
Affiliation: Cleveland Clinic Foundation, Cleveland, OH

Introduction: Preliminary data indicated[1] that oral practice examination (OPE) scores in a large anesthesiology training program showed a pattern of weak correlation with selected clinical competence scores provided by the clinical anesthesia system of evaluation (CASE) method.[2] It was felt at the time that the weak correlations were most likely due to the small sample size and, in some cases, lack of continuity in the cumulative clinical competence scoring. In order to examine this question in a more rigorous fashion, the authors evaluated the association between all categories of the CASE method clinical competence scores and OPE results during a two-year period.

Methods: The procedure for administering the OPE at our institution closely resembles the format for the ABA oral examination. Twice yearly, on two consecutive days, three pairs of faculty examine approximately 40 residents during 30-minute sessions. Stem questions are assigned in a manner so as to eliminate prior knowledge of the exam content. Despite differences in stem question themes, the structure of the guided question is identical and organized into preoperative, intraoperative, postoperative and additional topics sections to ensure maximum uniformity. Each examiner independently grades the trainee by assigning an overall score, a subscore for each subset question and a deficiency score for clarity, judgment, application of knowledge and adaptability for each subset question. Clinical competence scores consisted of cumulative z-scores of negative faculty comments in the categories indicated in Table 1. Statistical analysis utilized correlations coefficients between each component of the clinical competence score and the overall, subset and deficiency scores from the OPE. Because of the large number of comparisons statistical significance was assumed at the p = 0.01 level. During the study period, a total of 97 residents were examined. Only first time exam takers and those with a complete and continuous set of clinical competence scores during their first nine months of training were included in the analysis.

Results: Of the 36 residents 15, 19, and 2 were at the CA1, CA2 and CA3 levels, respectively. Correlation coefficients between CASE categories and OEP total, sub- and deficiency scores were uniformly less than 0.5. In in only two comparison was the correlation statistically significant. (Preop subscore vs. CMP:r = -0.418; Preop-deficiency score vs. LFI: r = 0.437.)

Discussion: The lack of correlation observed in the present data may point to the possibility that an oral practice examination evaluates a different aspect of a trainee's performance than do daily clinical performance evaluations. Alternatively, our results may have been affected by motivational factors because results of the OPEs at our institution are not used in residents' program performance evaluation. It has been suggested that daily evaluations may not constitute a complete index of all residents performance.[3] If OPE results are used for evaluations purposes, we suggest that they be used in conjunction with other indicators of resident performance.

References:
1. Anesth Analg 70:S354, 1990
2. Anesthesiology 59:A465, 1983
3. Anesth Analg 70:S310, 1990

TABLE 1

MNG - MANAGEMENT
CIS - CRITICAL INCIDENTS
P/P - PRE/POST OP. EVALUATION
E/O - EFFICIENCY/ORGANIZATION
CMP - COMPOSURE
CNF - CONFIDENCE
TKS - TECHNICAL SKILLS
IPS - INTERPERSONAL SKILLS
TKI - TAKES INSTRUCTION POORLY
EAG - EAGERNESS TO LEARN
CNS - CONSCIENTIOUSNESS
KNW - KNOWLEDGE
LFI - LEARNS FAST/INTELLIGENT
BLV - BELOW LEVEL
UNE - UNETHICAL

S239

Title: **DO TEMPERATURE AND DILUTION AFFECT THE SEALABILITY OF PINHOLE ENDOTRACHEAL CUFF LEAKS?**

Authors: A. Schubert, MD; M. Walsh, MD and L. Ilyes, BS
Affiliation: Cleveland Clinic Foundation, Cleveland, OH

Introduction: Intraoperative endotracheal tube (ETT) cuff puncture may lead to morbidity from airway loss in surgical procedures where access to the face is limited. At room temperature, diluted 2% lidocaine jelly can effectively seal a small ETT cuff perforation, which permits continued positive pressure ventilation (PPV)[1]. In an effort to further define this technique, the authors studied the effect of body temperature, dilution and time on ETT cuff sealability and deflation.

Methods: Using a model of PPV via ETT (see figure), a reproducible needle cuff injury was induced. Baseline minute ventilation (MV) was measured at standard adult ventilator settings. Upon cuff puncture, six randomly selected "treatments" were applied. Group A (n=8) cuffs were insufflated with 100% 02 using a 25 mmHG "popoff" valve. Group B (n=8), C (n=8) and F(n=7) ETT cuffs were injected with, respectively, 1:1, 1:2 and 1:3 mixtures of 2% xylocaine jelly (Astra) and 0.9% saline. Groups D (n=8) and E (n=8) were identical to groups B and C, respectively, except that the trachea/ETT model was immersed in a water bath servo-controlled at 37°C. MV was recorded every 5 min after cuff puncture for 30 minutes, at which time the cuff was deflated. The volume of lidocaine retrieved and the time to cuff deflation were recorded. Wasted ventilation was calculated as the difference of extrapolated baseline MV and total treatment period ventilation. In a separate experiment, the cuffs of 16 intact ETTs were inflated with 8 ml of either 1:1 or 1:2 lidocaine/saline mix and immersed in a water bath at 37°C. Cuff deflation times and volume aspirated were recorded after 13 hours.

Results: Baseline MV and cuff inflation volumes were similar among all groups. All cuff punctures resulted in immediate deflation. Adequate MV was maintained in all ETTs except for one each in groups B and E showing leaks refractory to cuff reinflation. Wasted ventilation was statistically similar in all groups. Cuff deflation was faster at higher dilution and more complete at 37°C(see table). After 13 hours at 37°C, all cuffs were completely deflatable, regardless of dilution. However, deflation was faster in the 1:2 than the 1:1 dilution group(104±79 vs. 192±72 seconds; p=0.034).

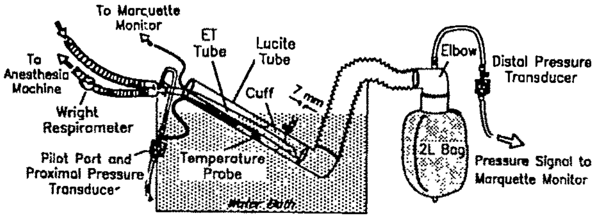
Discussion: Even at body temperature, diluted lidocaine jelly provides an effective seal of pinhole ETT cuff injury comparable to continuous cuff insufflation with O_2. Although one cuff failed to seal at the 1:2 dilution, the ability to deflate cuffs was superior when compared to the 1:1 mix. We suggest that the higher dilution could be considered for clinical use.

Reference: Anesthesiology 71:A466,1989

Table 1

Mix	Lidocaine (ml) Removed Injured Cuff[b] 21°C	Lidocaine (ml) Removed Injured Cuff[b] 37°C	Time[a] to Injured Cuff Deflation[b] 37°C
1:1	3.4 ± 1.0	5.1 ± 0.9*	187 ± 99#
2:1	5.8 ± 0.7	5.3 ± 0.5	47 ± 11

a:In Seconds; b:Mean + SD; *p<0.05 vs. 21°C; #p<0.05 vs. 2:1



S240

TITLE: THE EFFECT OF GASTRIC SUCTION ON POSTOPERATIVE NAUSEA AND VOMITING IN CHILDREN

AUTHOR: S.R. Schulman, M.D.

AFFILIATION: Departments of Anesthesiology and Pediatrics, University of California, Davis Medical Center, Sacramento, California 95817

Introduction. Postoperative nausea and vomiting in children is twice as common as in adults[1]. It is a major cause of both delayed discharge from the recovery room and unanticipated hospital admission. Factors contributing to postoperative emesis include anesthetic technique, duration and site of operation, and gastric inflation. Many experts advocate emptying the stomach prior to emergence[2]; however, the efficacy of this maneuver in children has not been studied. We sought to determine if emptying the stomach in an anesthetized child prior to emergence decreases the incidence of postoperative nausea and vomiting.

Methods. After obtaining approval from the institutional Human Subjects Committee, 59 ASA physical status 1 or 2 elective pediatric surgical patients (age 3 mos. to 14 yrs.) undergoing general anesthesia were studied. Children in whom nasogastric drainage was part of the surgical management and children undergoing ophthalmologic or ENT procedures were excluded from the study. No patient received prophylactic antiemetics. Anesthetic technique was left to the individual practitioner. Patients were assigned to a suction or no suction group. Patients in the suction group (N=26) had an orogastric tube placed just prior to emergence. Gastric contents were removed and the tube withdrawn before awakening. Correct tube placement was assessed by the ease of insertion and the pH of the aspirate. Patients in the no suction group did not undergo gastric intubation. The presence of nausea and vomiting in the first 24 hours postop was assessed by an observer blinded to the experimental design. The data were analyzed by the chi-square test.

Results. The results are illustrated in Figure 1. Twenty-six of the 59 patients (44.1%) underwent gastric suctioning, while 33 of 59 (55.9%) were not suctioned. Of the 26 patients whose stomachs were emptied, 11 (42.3%) vomited. Eighteen of the 33 children who were not suctioned (54.5%) vomited. These differences (42.3% vs 54.5%) were not statistically significant (chi-square = 0.450)

Discussion. Results of the present study suggest that gastric suctioning prior to emergence does not affect the incidence of postoperative nausea and vomiting in children. Many factors influence the incidence of emesis in the perioperative period. Further large scale studies which control for anesthetic technique are needed to resolve the question of whether gastric suction significantly affects postoperative nausea and vomiting in children.

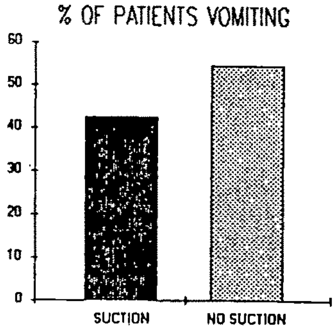


FIGURE 1

References.

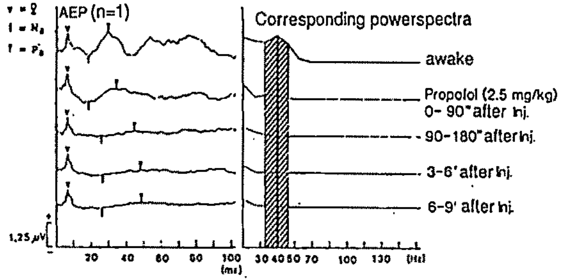
1. Palazzo MGA, Strunin L. Can Anaesth J 31:178-187, 1984.
2. Motoyama EK (ed). Smith's Anesthesia for Infants and Children, 1990; 322.

S241

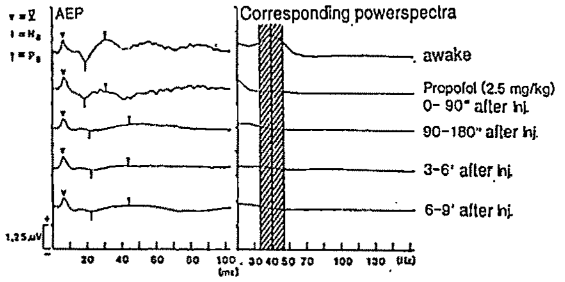
PROPOFOL SUPPRESSES NEURONAL OSCILLATIONS IN AUDITORY EVOKED POTENTIALS

D.Schwender[1]M.D.,Ch.Madler[1]M.D.,I.Keller[2]Ph.D.,E.Pöppel[2]Ph.D.
[1]Institute for Anesthesiology and [2]Med. Psych., University of Munich, 8000 Munich 70, FRG

Neuropsychological and neurophysiological investigations indicate that a 30-40 Hz oscillatory brain mechanism is necessary for the adequate uptake and processing of elementary successive sensory events. An oscillatory component of that particular frequency range can be observed in the mid-latency auditory evoked potentials (MLAEP). Because general anesthesia may be defined as a suppression of sensory information processing, the effect of Propofol on MLAEP and auditory evoked neuronal 30-40 Hz oscillation was studied. After institutional approval and informed consent in 16 patients scheduled for minor gynecological procedures anesthesia was induced with Propofol (2,5 mg/kg b.w. i.v.). Auditory evoked potentials were recorded before, during and after induction of general anesthesia on vertex (positive) and mastoides on both sides (negative). Auditory clicks were presented binaurally at 70 dBnHL with a frequency of 9,3 Hz. Using the electrodiagnostic system Pathfinder I (Fa. Nicolet) 1000 successive stimuli were averaged over a 100 ms poststimulus period and analysed off-line. Latencies of the peaks V, Na, Pa were measured. By Fast-Fourier-Transform-Analysis corresponding powerspectra were calculated to analyse energy portions of the AEP frequency components. In the awake state AEP showed an oscillatory component between 20 and 100 ms poststimulus latency. Corresponding powerspectra indicated a dominant 30-40 Hz frequency. After induction of general anesthesia with Propofol there was a statistically significant increase in peak-latencies Na, Pa, neuronal 30-40 Hz oscillation became suppressed and the energy maximum of the AEP shifted to the low frequency range (see fig. 1). The results support the concept that the underlying framework of sensory information processing is a stimulus-dependent, oscillatory brain mechanism. General anesthesia with propofol suppresses oscillatory brain mechanisms necessary for adequate sensory information processing. This observation may indicate a functional neuropsychological and neurophysiological mechanism, which could produce the state "general anesthesia". AEP monitoring could be a useful tool to monitor central pharmacodynamical anesthetic effects.



Grand Avcrage (n=16)



S242

OCFENTANYL IN BALANCED ANESTHESIA: COMPARISON WITH FENTANYL

PS Sebel MB, MR Murphy MD,
J Fletcher MB, S Mick RN
Department of Anesthesiology
Emory University Medical School, Atlanta, GA

Ocfentanyl (OC) is a piperidine derivative, which, in volunteers, is approximately 200 times more potent than morphine.(1) We report here the first clinical study of OC as a supplement during balanced anesthesia, compared double-blind with fentanyl (F).

Following Human Investigations approval, 60 consenting patients, ASA I-III were randomly allocated to four equal groups: OC 1 µg/kg, 3 µg/kg, 5 µg/kg, F 5 µg/kg. Following premedication with diazepam 10 mg orally, baseline cardiovascular measurements were made and the opioid injected double blind over 20 secs. Forty seconds later thiopental 2 mg/kg was administered followed by 50 mg every 15 secs until loss of lash reflex. Vecuronium 0.1 mg/kg was used to facilitate endotracheal intubation. N_2O/O_2 (FiO_2 0.4) was administered. Blood pressure and heart rate were measured every minute after injection of opioid until 20 min and every 5 min thereafter. Isoflurane was started when blood pressure or heart rate was 20% above baseline value. Data are mean ± SD. Statistical analysis was with repeated measures ANOVA or 't'-test as appropriate.

Duration of action of OC (measured by time to isoflurane) was not significantly different between groups although there was a trend towards longer duration of action in the higher doses (Table). Two patients in the OC 5 µg/kg did not require isoflurane. There were no differences in pentothal requirement between groups. There was a statistically significant difference between groups in hemodynamic responses to intubation, systolic blood pressure increased from 127.9 ± 26.8 to 183.3 ± 28.5 mmHg and heart rate from 82 ± 18.4 to 103 ± 24.7 beats/min in the OC 1 µg/kg group. There were no differences between the OC 3 and 5 µg/kg group and F 5 µg/kg group.

The hemodynamic responses seen in the OC 1 µg/kg group suggest that it is inadequate as a supplement to general anesthesia. No difference could be determined between the OC 3 and 5 µg/kg group and F 5 µg/kg group. No dose response relationship between OC 3 and 5 µg/kg could be demonstrated. The larger doses, not being associated with increased duration of action or better hemodynamic stability. These data suggest that ocfentanyl has no significant advantage to fentanyl as a supplement to general anesthesia.

REFERENCES:

1. Anesthesiology 71:A321, 1989.

TIME TO START ISOFLURANE AND THIOPENTAL REQUIREMENT

	min	mg/kg
OC 1 µg/kg	19.5(31.3)	3.2(1.2)
OC 3 µg/kg	27.5(23.7)	2.9(0.8)
OC 5 µg/kg	29.3(18.9)	2.6(0.8)
F 5 µg/kg	20.7(21.1)	2.9(0.7)

Data are mean (SD)

S243

CHARACTERIZATION OF A MUTATION AFFECTING SENSITIVITY TO VOLATILE ANESTHETICS IN C.ELEGANS

Authors: Margaret M. Sedensky, M.D.; Philip G. Morgan, M.D.
Affiliation: Dept. Anesth., University Hospitals, Cleveland, OH

INTRODUCTION: We demonstrated that multiple sites of action for volatile anesthetics (VAs) exist in the nematode, C. elegans (Ce)(1); Nash et al independently have obtained similar results in Drosophila(2). We have identified five genes which alter at least two of these sites. Mutations in two of these genes, unc-79 and unc-80, increase the sensitivity of this nematode to four VAs. However, neither of these mutations increase the sensitivity of Ce to enflurane (E) or isoflurane (ISO).

We have isolated new mutations which show altered sensitivities to ISO or E. These mutations may represent alterations to sites of anesthetic action other than previously identified. We are determining the nature of these other sites of action of VAs in Ce.

We have cloned part of the unc-80 gene, and are in the process of determining the nucleotide sequence of this gene. This will allow us to determine the amino acid sequence of the protein encoded by this gene and is an important step in determining its function.

METHODS: New mutations(alleles) were isolated by exposing the normal strain (N2) to ethylmethanesulfonate. Mutants were then screened in concentrations of ISO or E previously shown not to anesthetize N2, unc-79 or unc-80. Nematodes anesthetized at these concentrations were used to generate isogenic strains, and the new mutations mapped.

A 1800 base pair (bp) fragment of the unc-80 gene was identified and ligated into the plasmid pBS. The resulting plasmid (pCW4) was identified and isolated by standard techniques. Since the fragment contained regions of unique and repetitive sequences (see results), these regions were subcloned into the new plasmids pCW2 and pCW3, respectively. Sequencing was performed using standard techniques.

RESULTS: We have identified seven new mutations which increase the sensitivity of Ce to ISO. Four of these mutations are new alleles of the previously described genes unc-79 or unc-80. In addition we have identified two new mutations which increase sensitivity to E; one of these is a new allele of unc-79. Thus, the new alleles of unc-79 and unc-80 have different profiles of sensitivities to VAs than the originally described alleles.

The restriction map for the 1800 bp fragment of the unc-80 gene is shown below. Region I contains a repeated sequence while region II contains only unique sequence. Initial data (not shown) indicates that DNA from both regions is compatible with coding sequence. At present we have not identified any homologies to other genes.

DISCUSSION: We have isolated new alleles of unc-79 and unc-80 having different patterns of sensitivities to anesthetics. This indicates that mutations at different locations in one protein may affect interactions with different groups of VAs. Thus distinct sites on one protein may interact with different VAs. Determining the structure of these proteins and the position of mutations conferring different patterns of sensitivity should give us information about what constitutes an anesthetic site of action. The sequence data for unc-80 may allow such an interpretation.

REFERENCES: 1. PNAS 87;2965, 1990. 2. PNAS, In Press.

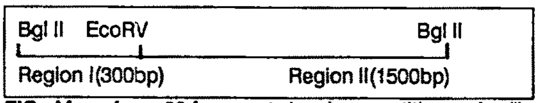


FIG. Map of unc-80 fragment showing repetitive region(I) and unique region(II). Restriction sites listed above the fragment.

S244

Title: LONG TERM ADMINISTRATION ALTERS THE PHARMACOKINETICS OF VECURONIUM

Authors: V Segredo MD, JE Caldwell MBChB, ML Sharma PhD, LD Gruenke PhD, RD Miller MD
Affiliation: Department of Anesthesia, University of California, San Francisco, CA 94143

Introduction. Following long-term administration of vecuronium to patients in the intensive care unit (ICU), prolonged neuromuscular blockade may occur after drug administration is discontinued(1). We believe this prolonged blockade may have a pharmacokinetic basis (2). Because ICU patients are such a heterogeneous group, comparisons between patients are difficult. In this study we attempted to overcome the problem of heterogeneity by studying the pharmacokinetics of vecuronium at two different times in the same patient: first, after the initial dose, and second, after vecuronium had been administered for at least three days consecutively.

Methods. After approval by our Committee on Human Research, and obtaining written consent, we studied 4 ICU patients who required prolonged neuromuscular blockade. Pharmacokinetics of the initial dose of vecuronium were studied after administration of a short infusion (10 to 25 min, 6.7 µg/kg/min). Vecuronium plasma concentrations were determined at intervals for 360 min. Pharmacokinetics after long term administration were studied by changing the mode of vecuronium administration from repetitive boluses to a 12-h-long constant infusion to provide a steady plasma concentration. The infusion rate was equivalent to the average rate of administration for the 24 hours prior to the study. Before stopping the infusion, 3 blood samples were withdrawn at 10 min intervals to confirm that the concentration was stable and to measure plasma clearance of vecuronium. Thereafter the infusion was stopped and vecuronium plasma concentrations were measured for 360 min. Plasma clearance (Cl), volume of distribution (Vd_{area}), and elimination half-life ($T_{1/2\beta}$) were calculated from standard formulae(3). Pharmacokinetic parameters were compared by paired t test; $P < 0.05$ was considered significant.

Results. While plasma clearance of vecuronium did not change after long term administration, $T_{1/2\beta}$ and Vd_{area} increased approximately threefold (see table)

Discussion. Our results suggest that there is no consistent change in the clearance mechanisms of vecuronium following long-term administration. We do not consider that the increase in Vd_{area} represents a physiological change. Rather, it is more likely that, compared to a single dose, after long-term administration a greater proportion of vecuronium is distributed to an already existing, slowly equilibrating compartment.

PHARMACOKINETIC PARAMETERS OF VECURONIUM AFTER INITIAL ADMINISTRATION (A) AND AFTER LONG TERM ADMINISTRATION (B).

	Plasma Clearace (ml/kg/min)		Vd_{area} (l/kg)		Elimination Half-life (min)	
Patient	A	B	A	B	A	B
# 1	4.0	1.6	0.25	0.46	44	197
# 2	4.6	3.7	0.42	0.90	63	170
# 3	2.6	3.2	0.18	0.78	47	167
# 4	3.5	4.4	0.45	1.42	90	223
	3.7±0.8	3.3±1.2	0.32±0.13	0.89±0.20*	61±21	189±26*

* $P < 0.05$ A *versus* B.

References. 1. Segredo et al. Anesthesiology 72,566, 1990. 2. Segredo et al. Anesth. Analg. 70:S361, 1990. 3. Gibaldi M, Perrier D. Pharmacokinetics. New York: Dekker, 1982.

S245

TITLE: ELECTROMYOGRAPHIC ANALYSIS OF TREMOR PATTERNS DURING EPIDURAL ANESTHESIA

Authors: DI Sessler, M.D. and J Hynson, M.D.
Affiliation: Department of Anesthesia, UCSF, CA, 94143

We have previously demonstrated that shivering-like tremor during epidural anesthesia in non-pregnant volunteers is preceded by central hypothermia and peripheral vasoconstriction,[1] does not result from stimulation of epidural/spinal thermal receptors,[2] and is not caused by systemic absorption of epidurally administered anesthetic.[3] In this study, we compared patterns of involuntary muscular activity during epidural anesthesia with those produced by normal shivering.

With IRB approval, chloroprocaine epidural anesthesia (≈ T4 sensory dermatome) was induced in 5 healthy volunteers. In 6 other volunteers, shivering was induced by central venous infusion of ≈ 4 L iced saline. EMG signals from the pectoralis and trapezius muscles were analyzed in each group using a previously described system.[1] We quantified the synchronous, 4-10 cycle/min "waxing-and-waning" pattern which characterizes normal shivering,[4] and searched for the abnormal tremor patterns sometimes occurring after general anesthesia.[5]

All volunteers demonstrated severe tremor. Muscular activity during epidural anesthesia and hypothermia-induced shivering had similar patterns. Both showed slow "waxing-and-waning," with ≈70% of the EMG power in the 4-10 cycle/min range. The correlation between muscles in different areas was similar in each group. Abnormal EMG patterns (*e.g.*, "spontaneous clonus" or "tonic stiffening") were not observed.

We have previously demonstrated that tremor during epidural anesthesia is thermoregulatory.[1] These data indicate that it has EMG characteristics similar to those produced by normal cold-induced shivering. We thus conclude, that tremor during epidural anesthesia is normal shivering, triggered by central hypothermia.

References.

1. Sessler DI, Ponte J. Anesthesiology 1990;72:816-821.
2. Ponte J, Sessler DI. Br J Anaesth 1990;54:731-733
3. Glosten B, Sessler DI, Östman PL, Faure E. Anesth Analg 1989;68:S102.
4. Israel DJ, Pozos RS. J Appl Physiol 1989;66:2358-2363.
5. Sessler DI, Israel D, Pozos RS, Pozos M, Rubinstein EH. Anesthesiology 1988;68:843-850.

Supported by National Institutes of Health grant #R29 GM39723.

S246

TITLE: ORAL PROPHYLAXIS OF ACID ASPIRATION SYNDROME: A COMPARISON OF FAMOTIDINE AND RANITIDINE

AUTHORS: A.L. Shafer, Pharm.D., A.R. Patil, M.D., J.A. Dewan, M.S.N., C.R.N.A., and R.L. Kirkman, M.D.
AFFILIATION: Departments of Anesthesia and Pharmacy, New England Medical Center, Boston, Massachusetts

Introduction Large volume, low pH gastric fluid increases the risk of aspiration during anesthesia. Ranitidine's effect on gastric pH during anesthesia is well documented. Equipotent doses of famotidine and ranitidine have not been extensively compared for this effect. This study compared single oral bedtime doses of famotidine (F), ranitidine (R), or placebo (P) on gastric pH and volume in healthy outpatient subjects at the time of induction (Ind) and emergence (Emg) from anesthesia.

Methods After approval by the IRB, informed consent was obtained from 42 patients randomly assigned to 1 of 3 groups (F 40mg, R 300mg, or P). Each subject was instructed to take the study substance at 10PM on the evening before surgery. The investigator was blinded to the substance received. Gastric fluid samples were obtained at the beginning and end of surgery for pH and volume determination. Analyses were performed by T-test and Chi Square (p<0.05 significant). Successful prophylaxis for each subject was based on pH >2.5 on both samples. Percent of subjects in each group with gastric volume >2.5mL on either sample was calculated.

Results No significant differences existed among groups regarding age, sex, weight or time from substance administration to either sample. Four subjects had no obtainable gastric volume at one or both sampling times. The fraction of subjects with any sample volume >25mL was 2/12 F, 6/16 R and 6/14 P. Results of gastric pH are shown:

Group:	F (N=12)	R (N=16)	P (N=14)
Avg pH Ind:	2.23±2.18	2.16±1.94	1.57±1.69[1]
Avg pH Emg:	3.12±2.77	3.92±3.47	2.42±2.08
# with pH >2.5 on both samples:	6(50.0%)	11(68.8%)[2]	3(21.4%)

1. P significantly different from F or R.
2. R significantly different from P.

Discussion Subjects receiving R or F had significantly higher pH values at induction than those receiving P, but the difference was no longer significant at the end of surgery. In examining the actual number of subjects with successful prophylaxis, only R appeared to offer significant protection over P throughout surgery. Of note: average pH rose in all groups during surgery, probably by a mechanism other than drug action. A larger population sample is necessary to draw definite conclusions. Our data support those of Dubin et al[1], suggesting that neither drug given as a single dose the evening before surgery reliably protects all patients against the effects of acid aspiration.

1. Anesth Analg 68:S72,1989.

S247

METHYLPREDNISOLONE DOES NOT AFFECT BRAIN EDEMA FOLLOWING HEAD TRAUMA IN RATS.

Y.Shapira MD, S.Cotev MD and E.Shohami PhD. Dept. of Anesthesiology Univ.of Washington, Seattle, WA. Dept. of Anesthesiology and Pharmacology, Hadassah Hospital and Hebrew univ. school of medicine, Jerusalem, Israel

We have previously described brain edema, following closed head injury (HT) in rats (1) by decreased tissue specific gravity and increased water content. The edema developed gradually in the contused hemisphere, starting at 15 min post HT, reaching maximal edema at 18h - 48h and returning to normal by 10 days. At the same time, the profile of prostaglandins (Pg) (2) changes showed increased production at 18h and return to normal by 10 days. In the present study methylprednisolone (M) was used in the same model to investigate wether it can affect the increased Pg's synthesis and edema formation, and improve neurological outcome .

Material and methods: Fifty six male Sabra rats (wt 320+48g) were divided into 7 groups(Gr). Gr 1-3 underwent sham operation and Gr 4-7 were traumatized. Gr 2,3,6 and 7 were treated with M. Gr 2,4,6 were sacrificed after 4h and Gr 1,3,5,7 after 24h. M was given intraperitoneally 30 mg/kg immediately after HT, 15mg/kg 2h later and then 15 mg/kg each 4h until sacrifice. A 24 point neurological severity score (NSS) was estimated 1h following HT and before sacrifice. Cortical slices from both hemispheres were taken to measure Pg's(E2,6-Keto-PGF-1a,TXB2) synthesis by radioimmunoassay and tissue specific gravity (SG) and H2O% as estimates of edema formation.

Results: There was a statistically significant (Spearman's test) correlation (R=0.427, P<0.01) between NSS and water content of the traumatized hemisphere (lt) for all groups, but no difference was found between the NSS of the four traumatized Gr's. There was a significant decrease (P<0.01 ANOVA) of SG and increase in H2O content of the lt hemisphere as compared to the rt in all traumatized Gr's, however no effect of M on SG was found. There was a good correlation between (Pearson's R=0.43 P<0.01) SG and water content. M treatment did not affect Pg's synthesis in traumatized rats.

Conclusion: M did not affect either Pg synthesis or brain edema, and it appears that it's clinical efficacy in our model can be ruled out.

1. Shapira et al., CCM 16:258,1988.
2. Shohami et al., JCBF 7:58,1987.

S248

Title: SUFENTANIL ANAESTHESIA HAS NO EFFECT ON CONDUCTION OF NORMAL AND ACCESSORY PATHWAYS IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

Authors: MD Sharpe FRCPC, JM Murkin FRCPC, WB Dobkowski FRCPC, C Murdoch FRACS, A Sharma FRCPC, G Klein FRCPC, G Guiraudon FRCPC, R Yee FRCPC

Affiliation: Departments of Anaesthesia, Cardiology and Cardiovascular Surgery, University Hospital, University of Western Ontario, London, Ontario

Introduction: Patients with Wolff-Parkinson-White Syndrome (WPW) undergoing accessory pathway (AP) surgical ablation require an anesthetic which has minimal electrophysiological (EP) effects on AP conduction since any depression may result in inadequate mapping and ablation.[1,2] Therefore this study evaluated the EP effects of sufentanil on accessory pathways in WPW patients.

Methods: With ethics committee approval, 12 WPW patients were studied. EP studies of antegrade and retrograde conduction were done pre-operatively in conscious patients as follows: 1) Right atrial refractory periods (RAERP), atrio-ventricular effective refractory period (AVERP), and accessory pathway effective refractory period (APERP) at cycle length 400/500 msec with coupling intervals in steps of 20 msec from 300-400 msec, and 10 msec below 300 msec; 2) Right ventricular effective refractory period (RVERP) at cycle length 400 msec; 3) Shortest cycle length (SCL) with 1:1 conduction for accessory pathway (SCL-AP)] conduction. On day of surgery, patients were premedicated with lorazepam (0.06 mg/kg, po) and morphine (0.1 mg/kg, im). Anesthesia was induced with sufentanil (20 μg/kg) and vecuronium (20 mg). After sternotomy, EP studies were repeated using epicardial hexapolar electrodes. Paired Student's t-tests compared EP studies before and during sufentanil anesthesia (significance - p<.05).

Results: Arterial blood gases, K^+, and body temperature remained within normal limits. All measured parameters were similar in both normal and AP conduction compared to pre-op EP studies(Table).

Discussion: Our results suggest that a premedication of morphine and lorazepam followed by a sufentanil anesthetic has no effect on the EP properties of normal and accessory pathways. We conclude, sufentanil anesthesia does not interfere with mapping and surgical ablation of AP.

References: 1. Anesth Analg 1990;70:S86.
2. Anesth Analg 1990;70:S365.

Table: ANTEGRADE CONDUCTION: (msec)

	# Pts	Control	Sufenta
RAERP	10	210 ± 29	221 ± 30
AVERP	5	272 ± 28	244 ± 26
APERP	6	311 ± 89	263 ± 68
SCL-AP	7	331 ± 98	393 ± 53

RETROGRADE CONDUCTION: (msec)

	# Pts	Control	Sufenta
RVERP	8	204 ± 26	191 ± 16
APERP	5	241 ± 25	212 ± 13
SCL-AP	8	338 ± 109	299 ± 50

(mean ± SD)

S249

Title: ANESTHESIA FOR THOROCOABDOMINAL AORTIC ANEURYSM: THE IMPACT OF CEREBROSPINAL FLUID DRAINAGE.

Authors: S.A. Shenaq M.D., P. Mohindra M.D.,
L. Svenssen M.D., E.S. Crawford M.D.

Affiliation: Department of Anesthesiology and Surgery
Baylor College of Medicine, Houston, TX

Despite the use of various shunts and adjuncts, paraplegia remains a devastating complication following resection of thoracoabdominal aortic (TAAA) aneurysm. Cerebrospinal fluid drainage (CSFD) has been shown to reduce the incidence of paraplegia in dogs. We performed a prospective randomized study to evaluate the effect of CSFD on the incidence of paraplegia. The study was approved by our institutional review board. One hundred patients undergoing (TAAA) resection who were at risk of developing paraplegia were randomized between CSFD (N = 51) and no drainage (N = 49). The two groups were similar regarding the etiology of the aneurysm, the clinical picture and the surgical technique.

Under local anesthesia, a radio opaque lumbar catheter with distal side holes was placed intrathecally (L_4-L_5 or L_3-L_4) for drainage and monitoring the CSF pressure. The catheter was advanced 20 cm from the skin.

Anesthesia was induced and maintained with fentanyl, pancuronium, midazolam and small percentage of isoflurane. A double lumen endotracheal tube was placed and ventilation was controlled (V_t= 10 ml/kg and respiratory rate of 10/min). In the CSF drainage group, 20 ml of CSF was drained prior to aortic clamping (AX). Additional CSF was drained to keep the CSF pressure below 15 mmHg during ACX to a maximum of 50 ml.

Systemic mean arterial pressure (MAP), heart rate (HR), Cardiac Output (CO), Pulmonary Cappillary Wedge (PCW), Central Venous (CV) and CSF pressures. were recorded after induction before and after aortic XC, after aortic unclamping and at the end of the procedure.

	MAP	CSF	CVP	CO	CI	SVR
Before Clamping	80	13	12	5.29	2.83	976.40
Immed. after Clamping	84.0	13	11	4.91	2.55	1226.97
15 " after Clamping	84	10	11	4.09	2.22	1326.70
Immed. after Unclamping	60	9	11	5.95	3.28	713.98
10 " after Unclamping	77	12	12	5.60	2.87	915.08
End of Surgery	84	11	13	5.44	2.94	1051.58

Paraplegia occurred in 24% of the drainage group and 19% in the control group. This study suggests that CSF drainage alone does not decrease the incidence of paraplegia following TAAA resections.

S250

TITLE: MECHANISMS OF BLOOD PRESSURE CHANGES FOLLOWING INFRA-RENAL AORTIC CROSS-CLAMPING

AUTHORS: K. Shibutani, M.D., T. Ogawa, M.D.,
S. Babu, M.D.* and P. Shah, M.D.*

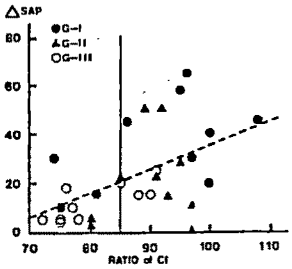
AFFILIATION: Dept. of Anes. & Surg.*, New York
Medical College, Valhalla, NY 10595

Conventionally, infra-renal aortic cross-clamping (AX) is believed to induce stress on the myocardium by increasing blood pressure and systemic vascular resistance (SVR). Recently, decreases in CO during AX were related to the decreases of the metabolic demand secondary to physiologic isolation of the lower part of the body.[1] If the former concept is correct, vasodilator therapy is needed during AX to maintain stable arterial pressure (AP). If the latter concept is correct, vasodilator therapy may not be needed when decreases in CO and metabolic demands are proportional. Therefore, with approval of Institutional Review Commitee, we examined the relationship between the metabolic demand and hemodynamic parameters induced by AX in patients anesthetized with fentanyl and N_2O (Group I, n=10). A second group (Group II, n=10) received an infusion of esmolol 150 µg/min. in addition to the fentanyl/N_2O/O_2 anesthetic. A 3rd group received a combination of epidural and light general anesthesia (Group III, n=10).

(1) Infusion of nitroglycerin was necessary to prevent hypertension in 6 patients in GI and none in GII and GIII. (2) Calculated oxygen uptake ($\dot{V}O_2$) decreased 15% following AX. Mean decreases in cardiac index (CI) were also approximately 15%. Systemic vascular resistance index (SVRI) following AX were re-calculated based on the assumption of a 15% decrease in body size. There were no significant increases in SVRI in GII or GIII. Increases in systolic arterial pressure (△ SAP) following AX were correlated with the ratio of post-AX CI to pre-AX CI.

Our data support the latter concept. Increasing the depth of anesthesia or combining epidural anesthesia with light general anesthesia could be an alternative method to prevent hypertension due to AX.

Reference: 1. Gelmans, et al: Am J Surg 155:378, 1988



		G-I	G-II	G-III
SAP (mmHg)	C AX	120±25 152±18*	128±24 149±24*	112±13 124±19
DAP (mmHg)	C AX	69±17 80±12*	69±11 72±11	59±12 59±11
CI (l/min.m^2)	C AX	2.7±0.5 2.3±0.4*	2.2±0.4 1.9±0.4*	2.2±0.4 1.8±0.4*
$\dot{V}O_2$ (ml/min.m^2)	C AX	96±21 83±14*	86±12 73±10*	86±23 74±20*
SVRI	C AX	2265±505 2802±531*	2827±628 3014±693	2418±575 2843±648

*:P<0.05 as compared to C

CALCUT[illegible]
CENTRAL LIBRARY

S251

TITLE: END-TIDAL CO_2: A CLINICAL NONINVASIVE CARDIAC OUTPUT MONITOR

AUTHORS: K. Shibutani, M.D., G. Whelan, N. Zung, M.D., P. Ferlazzo
AFFILIATION: Dept. of Anesthesiology, New York Medical College, Valhalla, NY 10595

In recent studies, changes in end-tidal carbon dioxide tension ($P_{ET}CO_2$) were closely related to corresponding changes in cardiac output (CO) during CPR. In this study, we evaluated the clinical usefulness of $P_{ET}CO_2$ as an indicator of CO by correlating the changes of $P_{ET}CO_2$ with hemodynamic changes. Under the approval of Institutional Review Committee, 4 patients undergoing infra-renal abdominal aneurysm surgery and 2 patients undergoing coronary artery bypass surgery were studied. Anesthesia consisted of 50% oxygen with air, and a continuous infusion of sufentanil 1-4μg/kg/hr. $P_{ET}CO_2$ was monitored with a Datex CO_2 monitor. The patient was ventilated with a constant tidal volume. Hemodynamic parameters were measured when $P_{ET}CO_2$ increased or decreased by more than 1 mmHg. There were 49 instances during the study when $P_{ET}CO_2$ increased or decreased by 1 mmHg or more. The changes of $P_{ET}CO_2$ and corresponding changes of hemodynamic values are shown in Table 1. Episodes of increases in $P_{ET}CO_2$ were related to surgical incision, light anesthesia or blood transfusion. Episodes of decreases in $P_{ET}CO_2$ were related to blood loss and increases in the rate of sufentanil infusion. There was a highly significant positive correlation between the increases or decreases in $P_{ET}CO_2$ (ΔCO_2) and the CO changes (ΔCO) (r=0.72, p<0.001) (Fig. 1).

Previously, we reported that during blood withdrawal, mixed venous pH and PCO_2 were statistically unchanged.[1] Thus, total amount of CO_2 returning to the heart is proportional to the CO. Therefore, the changes of $P_{ET}CO_2$ are expected to reflect changes of CO during the periods of transient hemodynamic changes, if ventilation is maintained constant. Our observations confirm the clinical usefulness of $P_{ET}CO_2$ as a non-invasive index of the changes of CO in a clinical setting when ventilation is kept constant.

References: Shibutani K, et al: ASA Annual Meeting, 1990.

Fig. 1

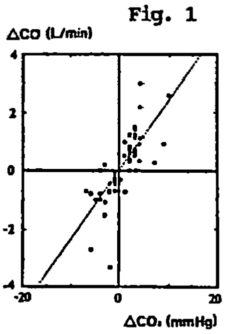


Table 1

	Increased PETCO2 (n=27) Before	After
PETCO2 (mmHg)	27.1± 4.3	30.4± 4.82*
CO (l/min)	3.1± 1.1	4.0± 1.3*
MAP (mmHg)	76.5±16.1	88.6±13.1
MPA (mmHg)	17.0± 7.8	19.6± 4.2*
	Decreased PETCO2 (n=22) Before	**After**
PETCO2 (mmHg)	28.36±4.17	15.36±3.85*
CO (l/min)	4.1± 1.5	3.3± 1.3*
MAP (mmHg)	86.1±10.7	74.5±15.2
MPA (mmHg)	21.1± 4.4	17.6± 4.3*

*, change significant, P<0.001

S252

Title: MODIFICATIONS ENGINEERED INTO RECOMBINANT HEMOGLOBIN DECREASE TOXICITY AND IMPROVE EFFICACY IN RATS.

Authors: S. Shoemaker, M.D., S. Hoffman, Ph.D., M.D., G. Stetler, Ph.D., D. Looker, Ph.D.

Affiliation: Somatogen, Inc. Broomfield, Colorado 80021.

Recombinant DNA techniques have been used to produce human hemoglobin (Hgb) in *E.coli*. By modifying the DNA in the globin genes, it has been possible to engineer changes in recombinant hemoglobin (rHgb) to address the two primary limitations in using stroma free human hemoglobin clinically: The first being the tendency for Hgb tetramers to dissociate into alpha-beta dimers and the second being the increased oxygen affinity which results when Hgb is removed from red cells and 2-3 diphosphoglycerate is lost. Alpha-beta Hgb dimers are readily filtered by the kidneys (in contrast to tetramers), resulting in a shortened plasma half-life and contributing to organ toxicity. Increased oxygen affinity may limit the ability of Hgb to offload oxygen in the capillaries. A rHgb has been produced which is genetically stabilized (cross-linked) and has a P_{50} of 30 mmHg, similar to the P_{50} of fresh, whole blood. Initial animal studies have been performed in rats to assess the safety and efficacy of rHgb as an oxygen carrying molecule. Study protocols were approved by the Animal Safety Committee and conducted at the University of Colorado Health Sciences Center. The first study was designed to assess whether genetic cross-linking of rHgb: 1) increased plasma half-life and 2) decreased renal toxicity. Two groups of rats were given rHgb intravenously. The first group received a rHgb which was cross-linked and the second group received a rHgb which was not cross-linked. Serial plasma Hgb levels were measured. To assess renal toxicity, blood chemistries were measured before (baseline) and one day following the administration of rHgb in both groups. In addition, the kidneys were evaluated histologically. It was found that genetic cross-linking doubled the plasma half-life (Figure 1) and decreased renal (Figure 2) toxicity. A second study was designed to assess whether rHgb could support oxygen transport in a rat with an otherwise lethal hematocrit (Hct). Total exchange transfusions were performed in two groups of rats. One group was exchanged with rHgb and the second group with human serum albumin (HSA). The post-exchange Hcts in both groups were ≤6%. Throughout the exchange, the rats in the rHgb group maintained normal arterial blood pressures and bicarbonate levels, in contrast to the rats in the HSA group which exhibited hypotension and developed a metabolic acidosis by the end of the exchange. Blood oxygen content measurements were higher in the rHgb group than in the HSA group. In summary, these preliminary studies demonstrate that rHgb produced in *E.coli* can be engineered to increase plasma half-life, decrease organ toxicity, and support oxygen transport in a rat model. rHgb may be an alternative to red cell transfusions.

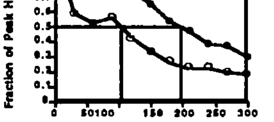


FIGURE 1

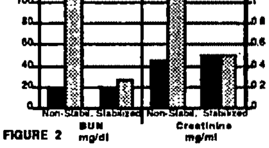


FIGURE 2

S253

TITLE: ASSESSMENT OF PATIENT POSITION FOR FIBEROPTIC INTUBATION USING VIDEOLARYNGOSCOPY

AUTHORS: GD Shorten M.D., HH Ali M.D., JT Roberts M.D.
AFFILIATION: Department of Anesthesia, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Introduction: Fiberoptic techniques which facilitate endotracheal intubation are widely used. The factors which hinder such techniques differ from those which make standard direct laryngoscopy and intubation difficult. In particular, the fiberscope cannot directly elevate the epiglottis, thus improving the view of the larynx. In this study we examined the influence of the position of the patient's head and neck on the fiberscope view of the laryngeal inlet using videolaryngoscopy.

Methods: With the approval of the institutional Human Studies Committee and having obtained informed consent, 20 consecutive patients (ASA class I or II) presenting for lithotripsy to renal calculi under general anesthesia were studied. Having induced anesthesia (thiopentone 5 mg/kg) and achieved muscle relaxation (succinylcholine 1 mg/kg), an Olympus BF 20 fiberscope was passed orally until the best view of the laryngeal inlet was obtained. Initially, the patients were positioned supine with the cervical spine in a neutral position i.e. no pillow. Having obtained the best view as described, the atlanto-occipital joint was maximally extended. In both of these positions laryngeal appearance was recorded using an Olympus OTV-F2 videocamera and graded as follows.

Grade I - epiglottic tip in contact with posterior pharyngeal wall.
Grade II - epiglottic tip not in contact with posterior pharyngeal wall but laryngeal structures not visible
Grade III - Posterior larynx (i.e. arytenoids, posterior vocal cords) visible
Grade IV - Most or all of laryngeal inlet visible.

Results:

Grade	Cerv-Spine neutral	Cerv-Spine extended
I	9	1
II	6	4
III	2	4
IV	3	11

Discussion: Clearly, atlanto-occipital extension improves the view of the laryngeal inlet obtained using an oral fiberoptic technique by lifting the epiglottis from the posterior pharyngeal wall. Previously, we documented that extension of the cervical spine produces a similar beneficial effect. Optimal positioning for fiberoptic laryngoscopy (cervical spine extension and atlanto-occipital extension) differs from optimal positioning for direct laryngoscopy (partial cervical flexion and atlanto-occipital extension).

S254

Title: STELLATE GANGLION ABLATION, HEMODYNAMIC AND METABOLIC IMPAIRMENT, AND ACUTE CORONARY HYPOPERFUSION IN DOGS

Authors: A Sidi, MD; JM Pool, BS; W Rush, BA
Affiliations: Dept. Anesth., Univ. of Fla. Col. of Med., Gainesville, FL 32610-0254

Stellate ganglion (SG) blockade reduces sympathetic tone of the myocardium. We studied the effect of SG ablation (SGA) during variable left anterior descending artery (LADa) constriction.

In 20 dogs (with institutional approval), anesthetized (barbiturate infusion) and ventilated, the pulmonary artery (PA), aorta (Ao), left ventricle (LV), left anterior descending artery (LADa) and vein (LADv), and circumflex vein were cannulated. LADa flow was measured (flowmeter) and constricted (micrometer) to 50% or 75% of resting flow for 15 min with 1 hr of normal flow between each. In 9 dogs, the left SG was stimulated and then removed surgically. Heart rate (HR), ECG, LADa flow, LV first time derivative (LV dP/dt), and Ao (AoP), PA (PAP), LADa, and LV (LVP) pressures were recorded continuously. Cardiac output (CO) (thermodilution) and regional myocardial blood flow (RMBF) (microspheres) were measured and blood was sampled before all constrictions (baseline) and before and after each for electrolyte and blood gas analysis.

Baseline hemodynamic and metabolic variables before manipulations did not differ significantly between the 2 groups. HR, AoP, and systolic LVP were lower after SGA than before it. SGA did not affect RMBF or its endocardial/epicardial ratio in the ischemic or nonischemic areas but, in the ischemic area, decreased lactate formation and production (= less negative extraction, consumption, and flux); the last 2 depended on LADa flow and RMBF. During constriction, electrolytes and glucose concentrations and extractions in both areas were similar.

SGA or SG blockade may decrease O_2 demand and, thus, myocardial O_2 consumption and lacate formation, which can benefit patients with ischemic heart disease who undergo surgery and general anesthesia.

Table. Effects of SGA During LADa Constriction

Group	Before All Constrictions	During Constriction	
		50%	75%
	Heart Rate (beats/min)		
Control	146.4 ± 8.6	143.3 ± 8.2	132.9 ± 9.7
SGA	121.1 ± 4.2*	116.7 ± 5.2*	110 ± 6.1*
	Systolic LV Pressure (mmHg)		
Control	144.4 ± 7.0	146.7 ± 5.2	131.1 ± 11.2
SGA	115.6 ± 4.9*	122.8 ± 6.1*	113.9 ± 8.2*
	LADv Lactate (mmole/L)		
Control	1.3 ± 0.2	2.7 ± 0.3†	3.5 ± 0.5†
SGA	1.3 ± 0.2	2.0 ± 0.4†	2.1 ± 0.4*†
	Ischemic Area Lactate Flux (mmole/min/100 g x 10^{-3})		
Control	43.4 ± 24.3	-71.0 ± 17.1†	-53.1 ± 11.3†
SGA	28.5 ± 11.1	-23.3 ± 15.8*†	-23.9 ± 7.11*†

Values are means ± SEM; abbreviations are defined in the text. *$P < 0.05$ compared with control at the same time. †$P < 0.05$ compared with before all constrictions in the same group.

S255

Title: PROPOFOL(P) FOR TOTAL INTRAVENOUS ANESTHESIA (TIVA) WITHOUT NITROUS OXIDE OR NARCOTIC INFUSION

Authors: JN Siler MD, SM Fisher MD, P Boon RN
Affiliation: Hahnemann University, Department of Anesthesiology, Philadelphia, Pennsylvania

Introduction: P has been used for TIVA with narcotic infusions and/or N_2O.[1] This study compares the appropriateness of using P via TIVA without N_2O or narcotic infusion with a standard anesthetic technique for outpatients undergoing 1-2 hr surgical procedures.

Methods: After institution approval and patient consent 60 P.S. I-II, 18-60 y o adults were randomized into two groups. Group I received P 2.5 mg/kg iv followed by P infusion of 0.1-0.2 mg/kg/min while breathing 30% O_2 in Air. Group II received methohexital 1.5 mg/kg iv followed by isoflurane 1-3%, O_2 30% and N_2O 70%. All patients were monitored and received fentanyl 0.5-1 mcg/kg, vecuronium 0.1 mg/kg, glycopyrrolate 0.4 mg and neostigmine 2.5 mg iv. A Dosimeter was used to detect N_2O. An observer blinded to the anesthetic technique gave a digit substitution test preoperatively and postoperatively.

Results: There were no group differences regarding demographic data, induction time or anesthesia duration by Student's t test. Heart rate at 1,2,3 and 5 min after induction, at intubation and extubation and SBP/DBP 3 and 5 min after induction were less in Group I vs Group II, $p<0.05$. No vasopressors or anticholinergics were used. No differences occurred in recovery parameters after discontinuing N_2O or P (Table I). Postoperative nausea/vomiting were the same by Chi-sq and Fisher's exact test. There was less need for anti-emetics in Group I, $p<0.05$. The use of narcotics was similar. Dosimeter analysis revealed no measurable amounts of N_2O in the P O.R. environment, but 100% detectable amounts of N_2O in Group II O.R.'s; 60% measurable amounts were >25 ppm. No patient experienced awareness during anesthesia.

Discussion: TIVA can be administered by a syringe pump or intermittent bolus injection. Sophisticated equipment is not necessary. P infusion with N_2O when compared with isoflurane for outpatient arthroscopy found no differences regarding times for patients to open their eyes, return to preoperative performance of psychomotor tests, or be fit for discharge.[2] In this study, P without N_2O or narcotic infusion was effective for TIVA. Awakening was rapid. Significant cardiovascular changes occurring in the P group were clinically acceptable. Recovery parameters were not different between the groups. There were less antiemetics needed in the P group. TIVA avoids contamination of the O.R. environment with anesthetic gases.

References: 1. Anaesthesia 1988;43(S):2-22 2. Anaesthesia 1987;42:356-59

Table I. Recovery Data Mean±SD

	Group I (n=30)	Group II (n=30)	P-value
Response to verbal command	10±7	8±4	NS
Time to discharge	131±41	148±43	NS
Nausea/Vomiting	4/1	8/5	NS
Anti-emetics	1	6	<0.05
Narcotics	11	11	NS

S256

TITLE: BASAL INFUSION AS SUPPLEMENT TO PCA IN ORTHOPEDIC PATIENTS

AUTHORS: D.G. Silverman, M.D.; L.M. Preble, R.N.; D. Paige, R.N.; T.Z. O'Connor, M.P.H.; S.J. Brull, M.D.
AFFILIATION: Anes. Dept., Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

Introduction. Although the addition of a basal infusion (BI) to patient controlled analgesia (PCA) has not proved to be consistently effective for resting pain following abdominal surgery,[1] we postulated that it would prove to be highly beneficial to patients recovering from extensive orthopedic procedures. The following study was undertaken to compare patient pain and narcotic requirements following orthopedic surgery in patients receiving PCA with and without a BI.

Methods. After institutional IRB approval, 24 patients who underwent ankle reconstruction (AR), 32 who underwent back fusion (BF), and 23 who underwent total knee reconstruction (TK) were evaluated. Of the AR patients, 12 were selected by the current pain service attending (who was unaware of the present study) to receive PCA (1-1.5 mg morphine/dose, lockout = 6-10 min), and 12 were selected to receive PCA+BI (0.5-1.0 mg/hr). Of the 32 BF patients, 9 received PCA and 23 received PCA+BI; 12 TK patients received PCA and 11 PCA+BI. At 9 a.m. the next day, pain was assessed, in the presence of a blinded investigator, by visual analog scale (VAS) anchored with 0 as no pain and 10 as worst pain imaginable; and mean hourly narcotic usage was recorded. For each of the surgical techniques, the PCA and PCA+BI patients were compared with Wilcoxon rank sum test; $p<0.05$ was considered statistically significant.

Results. As noted in the table, for each procedure the patients who also received BI reported lower pain scores than those who received PCA alone ($p<0.05$ between PCA and PCA+BI for AR and BF). In AR patients, this was associated with a 0.7 mg/hr mean increase in narcotic usage. However, such an increase was not noted in BF and TK patients. BF patients actually used an average of 1.3 mg/hr less drug when their PCA was supplemented with BI.

Discussion. The data strongly suggest the value of adding a basal infusion of narcotic to PCA for treatment of postoperative orthopedic pain. The pain following many forms of orthopedic surgery tends to be persistent and thereby should benefit from the consistent level of analgesia provided by BI. If influenced at all by anesthesiology attending bias, the present data would tend to underestimate the value of BI in that a patient who was anticipated to have more pain would more likely have been assigned to the PCA+BI regimen. The greatest benefit of adding a BI to PCA may be that BI provides a continuous level of analgesia during sleep, while, in the PCA alone patients, the narcotic serum levels would be allowed to decrease to considerably below the analgesic threshold.

	VAS PAIN (0-10) Median	VAS PAIN (0-10) Range	Narcotic (mg/hr) Mean ± SD
AR: PCA	6.0	4-10	3.4±2
PCA+BI	*4.0	0-7	4.1±2
BF: PCA	6.0	3-9	5.4±5
PCA+BI	*4.0	2-9	4.1±2
TK: PCA	5.5	0-10	2.1±1
PCA+BI	4.0	0-6	2.3±1

* $p<0.05$ between PCA and PCA+BI

References:

1. Anesthesiology 71:502, 1989

S257

THE 'CONCEPT OF AUTOLOGOUS TRANSFUSION' - A PROSPECTIVE ONE YEAR'S STUDY IN OVER 4.000 ORTHOPAEDIC-SURGICAL PATIENTS

G. Singbartl, MD, PD, W. Schleinzer, MD
Dept. Anaesthesiology, Intensive Care and
Transfusion Medicine, Endo-Klinik, D-2000 Hamburg 50

While the risk of transmission of the HIV virus is extremely small, post-transfusion hepatitis still represents the most serious risk in patients receiving homologous blood. Additionally, blood transfusion bears the risk of immunosuppression, that might be important to patients undergoing an operations for malignancies. Based on these facts autologous transfusion techniques gain an increasing importance in the transfusion-management of surgical patients.

So far there are four methods avaible for routineous clinical use to reduce the need for homologous blood, namely: 1st acute normovolaemic haemodilution (NHD); 2nd intra-/postoperative autologous blood salvage (IBS); 3rd preoperative autologous plasmapheresis (PPH); 4th preoperative autologous blood donation (ABD). As each of these methods has limitations of its own, the most effective way to minimize the need for homologous blood is to combine these four blood-saving-techniques to the 'concept of autologous transfusion' (CAT).

Method:
This prospective one year's study (in 1989) has been performed in 4.357 ASA I-III patients aged between 24 and 89 years and undergoing major elective orthopaedic surgery in order to analyze the efficiency of the 'concept of autologous transfusion'. The data obtained for 1989 have been compared with those taken from 1986 and 1987. While in our department in 1986 and 1987 no autologous transfusion techniques at all had been applied, 1989 represents that year, in which the administration of the 'concept of autologous transfusion' has become a routineous measure.

As neither the team of the surgeons has changed nor did the kind of major operations and the corresponding operative techniques, this kind of analysis seems justified. Moreover, on ethical reasons no other way of comparison appears to be possible.

Contraindications have been classified as follows: NHD: aortic-stenosis, unstable angina, sepsis. IBS: infection, tumor operation. PPH and ABD: decompensation of the cardio-vascular, pulmonary or haematopoetic system, decompensated metabolic disorders, acute systemic infection, bacteraemia / sepsis. Overall, laboratory findings were to be within normal limits, i.e.: Hb >11.0g/dl; Hk >34.0 %; total protein content >60 g/l; prothrombin time (Quick) >70 %; PTT <40 sec. Age per se has been considered no contraindication for autologous transfusion techniques.

Results:
While the number of major orthopaedic operations increased by about 18 % (from 3.689 in 1986 to 4.357 in 1989) the need for homologous blood decreased by more than 80 % (from 12.500 units of packed red blood cells in 1986 to 2.145 units in 1989). This reduced need for homologous blood transfusion has been achieved both by applying NHD in 3.590 patients (= 82.4 %) and IBS in 1.926 patients (= 44.2 %) as well as by strictly applying preoprative autologous PPH (n= 5.279) and ABD (n= 2.261).

In 1.3 % preoperative autologous donations were accompanied by minor complications, i. e. in 1.0 % vaso-vagal reactions or collaptic episodes occured, treated by administering atropine as well as by an infusion of cristolloids or colloids. In 0.3 % anaphylactoid reactions(grade I and II) due to the colloid (gelatin) have been observed, necessitating the additional administration od H1-and H2-blockers. In no case there was danger of life, and each day-case patient coming to the autologous donation left for home on the same day.

Discussion:
The 'concept of autologous transfusion', i. e. consequently applying normovolaemic haemodilution and intraoperative blood salvage as well as preoperative plasmapheresis and autologous blood donation effectively reduce the need for homologous transfusions. In 4.357 patients undergoing major orthopaedic operations it resulted in a decrease of homologous transfusion by more than 80 %. In only 1.3 % minor side effects occured in day-case patients applying preoperative autologous plasmapheresis or autologous blood donation. The conclusion that can be drawn is, that the 'concept of autologous transfusion' is both a very effective and harmless method to reduce the need for homologous blood transfusions. It is the combination out of various autologous blood saving techniques so far available, that make the 'concept of autologous tranfusion' effective and attractive.

S258

TITLE: ELEVATED THERMOREGULATORY THRESHOLD FOR SWEATING DURING REWARMING FROM CARDIOPULMONARY BYPASS

Authors: R Sladen, M.D. and *DI Sessler, M.D.
Affiliation: VA Medical Center, Durham, NC, 27705, *Department of Anesthesia, UCSF, CA, 94143

General anesthesia decreases the thermoregulatory constriction threshold (central temperature triggering peripheral vasoconstriction) about 2°C.[1] The extent to which anesthesia increases the threshold triggering responses to hyperthermia in humans remains unknown. Accordingly, we tested the hypothesis that the sweating threshold is elevated during anesthesia.

With IRB approval, we studied 15 patients during cardiopulmonary bypass rewarming. Anesthesia was maintained with fentanyl and pancuronium. We measured nasopharyngeal and mean skin temperature, and laser Doppler perfusion on the tip of the nose (a thermoregulatory site). Sweating was qualitatively graded on a scale from zero to three; a score of two was considered significant.

Significant sweating was observed in 8 patients, 46 ± 15 min after the start of rewarming. Nasopharyngeal temperature was 38.1 ± 0.4°C and mean skin temperature was 31.7 ± 1.4°C when sweating started. The laser Doppler perfusion index increased 2-6-fold in the period from 15 min before to 15 min after sweating started. Rewarming was relatively slow: nasopharengeal temperature increased 0.4 ± 0.3°C in the 5 min before significant sweating was first detected. Sweating stopped when nasopharyngeal temperature decreased 0.7 ± 0.4°C and mean skin temperature increased 1.6 ± 0.9°C. The laser Doppler perfusion index decreased to 76 ± 27% in the period from 15 min before to 15 min after sweating stopped. Seven patients did not sweat at a maximum nasopharyngeal temperature of 38.6 ± 0.5°C and a corresponding mean skin temperature of 32.2 ± 0.7°C.

Rapid thermal perturbations precipitate regulatory responses better than slow alterations of similar magnitude. Thus, it is likely that the threshold would be slightly higher in patients rewarmed more slowly. Nonetheless, the thermoregulatory threshold for sweating was about 1°C above normal, compared with vasoconstriction which does not occur until patients are ≈2°C hypothermic. These data suggest that the general anesthesia disturbs thermoregulatory responses to excess heat less than those to hypothermia.

References.

1. Støen R, Sessler DI: Anesthesiology 72:822-827, 1990

Supported by National Institutes of Health grant #R29 GM39723.

S259

Title: COMPARISON OF THE POTENCY OF VECURONIUM AND ATRACURIUM IN CHILDREN USING THE EMG RESPONSE

Authors: M. Sloan, M.D., J. Lerman, M.D., FRCPC, B. Bissonnette, M.D., FRCPC
Affiliation: Dept of Anaesth and the Research Institute, The Hospital for Sick Children, Univ of Toronto, Toronto, Ontario, Canada

Introduction: The pharmacodynamics of vecuronium in children during halothane anesthesia has been previously evaluated.[1] Although the ED_{50} using the single bolus technique has been reported, the ED_{95} (the basis for determining the dose used in clinical practice) has not been established. Therefore we undertook this study to determine the potency of vecuronium in children during N_2O-O_2-halothane anesthesia and to compare it to that of atracurium.

Methods: After ethical committee approval and informed consent, 30 fasted and unpremedicated children were studied. All were ASA I or II, ranged in age from 2-9 years, and were scheduled for minor elective surgery. Children with a history of renal, hepatic or neuromuscular disease, or those in whom a difficult intubation was anticipated were excluded from the study. Patients were randomly assigned to one of six treatment groups (n=5 per group) to receive a single bolus dose of 0.02, 0.025, or 0.03 mg/kg of vecuronium or 0.075, 0.1, or 0.125 mg/kg of atracurium.

Anesthesia was induced with thiopental 5.0 mg/kg and fentanyl 2.0 µg/kg, and intubation was performed under halothane anesthesia without the aid of muscle relaxants. Anesthesia was maintained with 70% N_2O in O_2, halothane (1 MAC end tidal concentration), and incremental doses of narcotics. After a stable end tidal halothane concentration was maintained for at least 10 min, the ulnar nerve in the forearm was stimulated via surface electrodes using a Datex Relaxograph EMG monitor which delivered a supramaximal train-of-four (2 Hz for 2 sec) signal every 10 sec. The degree of neuromuscular blockade was determined by the height of the first twitch (T1) of the train-of-four as compared to control, and the EMG responses were recorded in a PSION LZ64 computer. When a stable EMG baseline was obtained, the designated dose of either vecuronium or atracurium was administered. The maximal depression of T1 was recorded, and the log dose-response curve for each drug was constructed using the probit method of Finney.[2] The ED_{50} and ED_{95} for each drug were calculated from the least squares linear regression equations. Statistical analysis ($p<0.05$ considered significant) was performed using one way ANOVA and the Student-Newman-Keuls test. The slopes of the regression lines were compared using an unpaired t-test.

Results: The results are summarized in Table 1. There were no significant differences in ages or weights of the six groups of patients. The slopes of the dose-response relationships were significantly different ($p<0.001$). The potency ratio of atracurium/vecuronium was 5.2 and 8.1 at the ED_{50} and ED_{95} levels respectively.

Discussion: We have determined the ED_{95} for vecuronium in children during N_2O-O_2-halothane anesthesia. It is less than that previously reported (0.06 mg/kg) using the cumulative dose technique.[3] This study also demonstrated that, in children anesthetized with halothane, the dose-response relationships of vecuronium and atracurium are not parallel.

References:

1. Anesthesiology, 58:519, 1983
2. *Probit Analysis*, 1952
3. Anesth Analg, 62:1083, 1983

Table 1: POTENCY OF VECURONIUM (VEC) AND ATRACURIUM (ATR)

Drug	Dose (mg/kg)	Peak Depression (%) (mean ± SD)	ED_{50} (mg/kg)	ED_{95} (mg/kg)
VEC	0.02	43.5 ± 19.0		
	0.025	66.8 ± 23.0	0.021	0.037
	0.03	84.0 ± 6.5		
ATR	0.075	25.6 ± 5.1		
	0.10	48.8 ± 25.0	0.11	0.30
	0.125	54.8 ± 23.7		

S260

TITLE: MILD HYPOTHERMIA ALTERS CORTICAL MAGNETIC MOTOR EVOKED POTENTIALS

AUTHORS: T. B. SLOAN, M.D., PH.D.

AFFILIATION: ANES. DEPT., UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO, SAN ANTONIO, TX 78284-7838

Magnetically induced cortical motor evoked potentials (MMEP) allow assessment of the spinal cord motor tracts. Interest in surgical monitoring prompted us to conduct an institutionally approved study to assess the effect of hypothermia on the EMG recordings of MMEP.

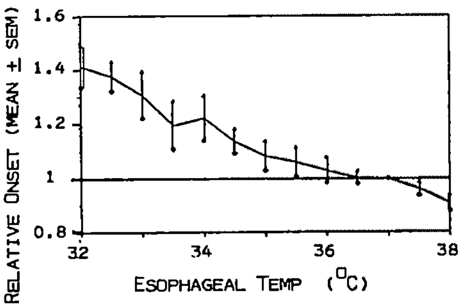
Six adult cynomologous monkeys (M fascicularis)(3.3-4.0 Kg) were anesthetized with ketamine (15-20 mg/kg IM followed by continuous infusion 10-15 mg/kg/hr). The trachea was intubated and ventilation supported. MMEP was elicited by a Cadwell MES-10 at supra-maximal intensity (70-80%) with the coil placed optimally over the scalp. The EMG response to MMEP was recorded from the opponens pollicus (elbow ground) using a Biologic Navigator (Filtration 10-3000 Hz, 1000 amplification).

The monkeys were randomly assigned to begin the study at either 38°C or 32°C as measured by an esophageal temperature probe. Surface heating or cooling techniques were used to alter temperature as needed. After baseline recordings were taken at the desired initial temperature, body temperature was gradually changed to the other extreme. Data was collected at 0.5°C intervals. At each temperature multiple stimulations were made to determine the threshold (% power) needed for stimulation, the amplitude (voltage from minimum to maximum peak) and shortest onset latency (time from stimulation to first deflection from baseline of the complex) when stimulated above the threshold. Data were analyzed by comparing the data with the averaged baseline recordings at 37°C.

Shown below are plots of the MMEP onset (mean ± SEM). As shown, onset increased linearly with a reduction in temperature. A tendency to increased threshold and lowered amplitude were also seen with temperature reduction.

This study suggests that MMEP monitoring under ketamine anesthesia, as measured by the EMG of the opponens pollicus, is well maintained during mild hypothermia. The increased onset time with hypothermia is consistent with reduced conduction velocity in the neural system. The increased threshold suggests the motor cortex may be less excitable when cool. These results suggest that body temperature alterations during surgery may cause MMEP alterations.

This study was funded by an Institutional Grant from the University of Texas.



S261

TITLE:	ALTERATIONS IN VENTILATION DOES NOT ALTER THE ONSET OF CORTICAL MAGNETIC MOTOR EVOKED POTENTIALS
AUTHORS:	T.B. SLOAN, M.D., PH.D. AND R. HICKEY, M.D.
AFFILIATION:	ANES. DEPT., UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO, SAN ANTONIO, TX 78284-7838

Magnetically induced cortical motor evoked potentials (MMEP) allow assessment of the spinal cord motor tracts. Interest in surgical monitoring prompted us to conduct an institutionally approved study to assess the effect of ventilation on the EMG recordings of MMEP.

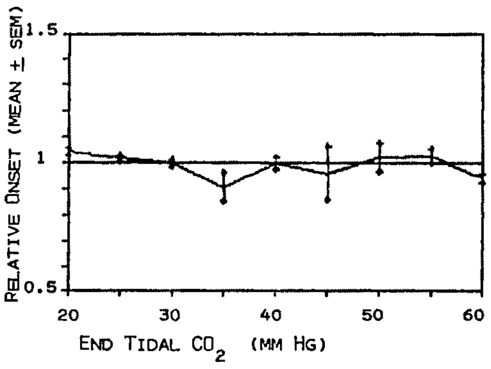
Ten adult cynomologous monkeys (M fascicularis)(3-5.4 Kg) were anesthetized with ketamine (15-20 mg/kg IM followed by continuous infusion 10-15 mg/kg/hr). The trachea was intubated and ventilation supported. MMEP was elicited by a Cadwell MES-10 at supra-maximal intensity (70-80%) with the coil placed optimally over the scalp. The EMG response to MMEP stimulation was recorded from the opponens pollicus (elbow ground) using a Biologic Navigator (Filtration 10-3000 Hz, 1000 amplification).

Animals were randomized to begin with hypo or hyperventilation and the ventilation adjusted to achieve the desired end tidal carbon dioxide (20 or 30 mm Hg). MMEP recordings of onset (time from stimulation to first deflection from baseline of the complex), amplitude (voltage from minimum to maximum peak) and threshold (% power needed for stimulation) were made and ventilatory rate adjusted to gradually change $ETCO_2$ to the other extreme. Data were recorded at intermediate ventilatory values. Venous and arterial blood gases were taken during the study to document ventilatory changes. Data were analyzed by comparing the results with the recordings at an $ETCO_2$ of 40 mmHg.

Shown below are a plot of MMEP onset (mean ± SEM) at various end tidal CO_2 concentrations. No significant change was seen over the range studied. Wide amplitude fluctuations were seen with little average change over the range studied. Stimulation threshold was increased above 45 mm Hg and at 20 mm Hg.

This study suggests that MMEP monitoring under ketamine anesthesia, as measured by the EMG of the opponens pollicus, is well maintained during ventilation between 20 mm Hg and 60 mm Hg end tidal CO_2. An increased power may be needed for stimulation at the extremes of this range.

This study was funded by an Institutional Grant from the University of Texas.



S262

TITLE: GLYCOPYRROLATE DOES NOT ATTENUATE THE HAEMODYNAMIC RESPONSE TO PROPOFOL

AUTHORS: J.R. Sneyd, M.D. & A. Berry, F.C.Anaes.

AFFILIATION: University Hospital of S. Manchester, Manchester M20 8LR, England.

INTRODUCTION: Induction of anaesthesia with propofol is often followed by a substantial reduction in blood pressure with minimum values recorded within two minutes of induction. When glycopyrrolate or atropine were given 5 min before induction and maintenance of anaesthesia with propofol and alfentanil, similar increases in heart rate were seen but, unlike atropine, glycopyrrolate reduced the fall in systolic and diastolic blood pressure at 3, 6 and 9 min after induction[1]. We have investigated the effect of three different doses of glycopyrrolate on the haemodynamic consequences of induction and early maintenance anaesthesia with propofol and fentanyl.

METHODS: With Ethical Committee approval and informed patient consent, female patients (A.S.A I-II) scheduled for elective breast or gynaecological surgery received glycopyrrolate 0 (n=24), 2.5 (n=25), 5 (n=25) or 7.5 (n=25) $mcg.kg^{-1}$, 5 min before induction of anaesthesia with fentanyl 1 $mcg.kg^{-1}$ and propofol (given until cessation of counting) followed by propofol maintenance at 10 $mg.kg.hr^{-1}$.

RESULTS: Although glycopyrrolate significantly increased heart rate in a dose related manner, the drop in blood pressure at 2 and 5 min after induction was similar in all groups (see table). Induction dose of propofol was 2.3 ± 0.1 $mg.kg^{-1}$ (mean ± S.E.M).

GLYCOPYRROLATE:	NIL	2.5 mcg/kg	5 mcg/kg	7.5 mcg/kg
-7 Min	95.2 ± 2.8	92.8 ± 3.7	93.1 ± 3	98.8 ± 2.9
-6	93.7 ± 2.5	92.3 ± 3.6	93.2 ± 2.9	99.8 ± 3.2
-4	92.3 ± 2.1	93.6 ± 3.3	93.4 ± 2.8	101 ± 2.4
-1	92 ± 2.7	93.4 ± 2.9	93.4 ± 2.6	101 ± 2.9
2	70 ± 2.1	71.5 ± 2.9	73.8 ± 2.8	76.3 ± 2.4
5	68.2 ± 1.8	68.6 ± 2.7	72.8 ± 2.3	76.6 ± 1.8

Mean Arterial Pressure (mm Hg) ± S.E.M. before and after induction. No significant between group differences (analysis of variance).

DISCUSSION: In view of the dose related increase in heart rate caused by glycopyrrolate and in the absence of data to support its use, we do not consider giving glycopyrrolate before induction of anaesthesia to be an effective stratagem to reduce the hypotension induced by propofol.

REFERENCE: 1. Skues et al. Anaesth Analg 1989; 69: 386-90.

S263

INFLUENCE OF COMBINED EPIDURAL/GENERAL ANESTHESIA ON THE HEMODYNAMIC RESPONSE TO MODERATE HEMORRHAGE IN A SWINE MODEL GW Snodgrass MD, FW Burgess PhD,MD, DE Brooks BS, CE Wade PhD, JA Scavone MD, WG Rodkey DVM. Letterman Army Medical Center and Institute of Research, San Francisco, CA 94129.

Introduction: Combined epidural/general anesthesia for major intraabdominal and thoracic operations is a subject of clinical debate regarding the increased requirement for intraoperative volume replacement and the potential for hypotension in high blood loss operations. To study the impact of combined epidural/general anesthesia on the hemodynamic response to perioperative hemorrhage we have developed a swine model

Methods: With the approval of the animal use committee, 15 Duroc crossbred swine were randomly allocated into three groups. All received general endotracheal anesthesia with halothane 50% nitrous oxide and oxygen. Pulmonary, carotid and femoral arterial catheters were inserted. A femoral venous catheter, cystostomy catheter and a T-14 epidural catheter were inserted. The splenic vessels were all ligated via a midline celiotomy. After a 30 min. equilibration period the control group received 7 ml of epidural saline. Group B-1 and B-2 received 7 ml of epidural 0.5% bupivacaine. Group B-1 received sufficient intravenous saline (mean of 15 ml/kg) to maintain the systolic blood pressure (SBP) within 20% of baseline. Group B-2 received intravenous saline (mean of 47 ml/kg) sufficient to restore the SBP to baseline over a 30 min. period. No additional fluids were administered after the initiation of the hemorrhage phase. Thirty minutes after the epidural injection all groups were bled 20% of their estimated blood volume over a 30 min. period via the femoral arterial line. Hemodynamic and plasma volume determinations were made at selected intervals up to 218 minutes.

Results: Baseline SBP, MAP, heart rate (HR), cardiac output (CO), and hematocrit (HCT) were comparable in all groups. Following epidural injection the HCT decreased 7% in group B-1 and 20% in group B-2 ($P<0.05$). SBP and MAP were lower than control but did not achieve significance. Following a 20% hemorrhage over 30 min. the SBP fell to 87 mmHg in the control, 61 in B-1 ($P<0.01$) and 67 in B-2 ($P<0.05$). The SBP and MAP for Groups B-1 and B-2 were significantly less ($P<0.04$) than the control group at 30 and 60 minutes post-hemorrhage. CO declined approximately 40% in all three groups post-hemorrhage and remained unchanged throughout the remainder of the experiment indicating a decline in peripheral vascular resistance. Plasma volumes (+/- SD) 30 minutes post-epidural injection for the control, B-1, and B-2 were 44(11), 50(15), and 63(16) ml/kg respectively. Thirty min. post-hemorrhage the plasma volumes declined to 35(7), 34(10), and 46(20)ml/kg, or 20%, 32%, and 27% of baseline. Repeat plasma volume determinations 3 hours post-hemorrhage were unchanged.

Discussion: General anesthesia combined with epidural anesthesia extending to a high thoracic level (T 1-4) produced an exaggerated hemodynamic response to a moderate hemorrhage. Aggressive volume loading and plasma volume expansion with crystalloid were unsuccessful at minimizing the degree and duration of the hemodynamic depression encountered.

S264

TITLE: VASOPRESSIN IS RELEASED WITH CATECHOLAMINES DURING ELECTROCONVULSIVE THERAPY

AUTHORS: S Soriano MD, J Benthuysen MD, D Fung MD
AFFILIATION: Dept. of Anesthesiology, University of California, Davis, CA 95616

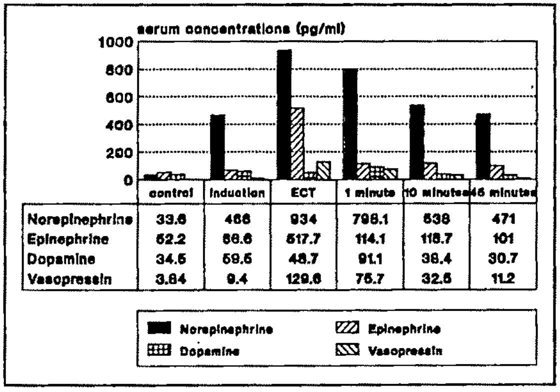
Introduction Electroconvulsive Therapy (ECT) related cardiovascular responses have been related to increases in epinephrine (E) and norepinephrine (NE),[1] while vasopressin (VP) responses have not been reported. We measured the VP and catecholamine (CAT) and cardiovascular responses in 5 patients during modified ECT.

Methods With Institutional Review Board approval, consenting ECT patients of ASA class I-III with major depression were studied. Monitoring included ECG (lead II) and arterial cannula for blood pressure and plasma sampling, and EEG (Neurotrac). Patients received either methohexital (1 mg/kg) or etomidate (0.3 mg/kg) followed by succinylcholine and 2 minutes of hyperventilation prior to ECT. Plasma samples were drawn preinduction, after induction, during seizure, and 1, 5, 15, and 45 minutes after the seizure. Systolic blood pressure in excess of 200 mmHg was treated with labetalol. E, NE, and dopamine (DA) were measured via HPLC, and VP was measured using radioimmunoassay. Changes in cardiovascular and hormonal responses were analyzed using ANOVA for repeated measures.

Results Mean arterial pressure increased significantly during and 1 minute following the seizure. Heart rate increased significantly during the seizure. NE and VP significantly increased during the seizure and 1 minute after, 2.1 and 36 fold respectively. E significantly increased 9.7 fold during the seizure. DA did not change. Seizure duration was 46.8± 9.6 seconds.

Discussion These results indicate that VP along with NE and E increases markedly during ECT. Given the direct vasoconstrictor effects of VP, the ability to control VP release during ECT perhaps merits study.

References.
1) Anaesthesia 36:795-799, 1981.



	control	induction	ECT	1 minute	10 minutes	45 minutes
Norepinephrine	33.6	466	934	798.1	538	471
Epinephrine	52.2	66.6	517.7	114.1	118.7	101
Dopamine	34.5	59.5	48.7	91.1	38.4	30.7
Vasopressin	3.84	9.4	129.6	75.7	32.5	11.2

S265

TITLE: EVALUATION OF A NEW LASER RESISTANT ANESTHESIA CIRCUIT PROTECTOR, DRAPE, AND PATIENT EYE SHIELD

AUTHORS: M. Sosis, M.D., Ph.D.
AFFILIATION: Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.

Although the shafts of combustible tracheal tubes may be protected from the surgical laser, conventional paper or cloth operating room drapes are flammable. Dermacare has designed protective shielding for the patient's eyes, the anesthesia circuit and a utility barrier drape; all for use during laser surgery. We tested the efficacy of these products under CO_2 and Nd-YAG laser fire.

A LaserSonics CO_2/Nd-YAG laser and operating microscope were used. The laser, in the continous mode of operation was set to 60 watts for the Nd-YAG and 70 watts for CO_2 laser study. Its beam diameter was 0.68 mm. The Dermacare laser safety eye shield, anesthesia circuit shield and personnel/anesthesia laser shield (drape) were tested by aiming first the Nd-YAG and then the CO_2 laser perpendicularly at five different areas on these three products. All tests were done in air.

Employing the Nd-YAG laser, the three products were unaffected by five trials of 1 min of laser fire at 60 watts. They were noted to be warm to the touch after laser exposure. Similarly, five trials with the CO_2 laser set to 70 watts caused no apparent change in the three products. However, CO_2 laser impingement onto the eye shield resulted in a reflection that caused the paper operating room mask of the laser operator to burn at a distance of three feet. All three products were again noted to be warm to the touch after 1 minute of CO_2 laser fire.

The combustion of disposable surgical draping material has been reported to produce copious smoke making it difficult for operating room personnel to breathe or see and it has necessitated the removal of an anesthetized patient from the operating room. Severe burns to patients have been reported. Disposable drapes are generally treated with a flame retardant, however once ignited, they are difficult to extinguish with water since it simply rolls off without effect.

To meet the need for a laser resistant operating room drape, eye shield and anesthesia circuit protector, Dermacare has developed aluminized products for these applications. The Dermacare eye shield is an opaque self adhesive mask shaped aluminized patient eye protector with integrated soft cotton eye patches. Our results show that it is impervious to the Nd-YAG or CO_2 laser under the conditions of this experiment, and should provide excellent protection during CO_2 or Nd-YAG laser surgery. It could however, reflect the laser with possible harmful effects. The Dermacare personnel/anesthesia laser shield is a utility drape that can be used anywhere in the operating room as a laser barrier. The aluminized material used in the construction of these products provided excellent protection even from direct and continuous output of the Nd-YAG or CO_2 lasers at high power.

S266

TITLE: SALINE-SOAKED PLEDGETS PREVENT CO_2 LASER-INDUCED TRACHEAL TUBE CUFF IGNITION

AUTHOR: M. Sosis, M.D., Ph.D.
AFFILIATION: Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Laser ignition of tracheal tubes during airway surgery presents a significant patient hazard. While the shafts of combustible tracheal tubes can be protected from the CO_2 laser by carefully wrapping them with metallic foil tape, the cuff remains unprotected. We performed a controlled evaluation of the recommendation that saline soaked pledgets be used to prevent laser induced tracheal tube cuff ignition.

Twelve Mallinckrodt (Glens Falls, NY) polyvinylchloride size 7.0 mm ID Hi-Lo tracheal tubes were studied. The tracheal tubes were each inserted into a 100 cc Pyrex graduated cylinder with a 2.5 mm ID which served as a "mock trachea." The tracheal tubes were connected to a circle anesthesia system and were flushed with 5L/min of oxygen for 5 minutes. The cuffs were then inflated with 20 cc of air and the system pressure was adjusted to 20 cm H_2O by adjusting the pop-off valve on the anesthesia machine. Six tracheal tubes (group 1) had 3 saline soaked Merocel (Mystic, CT) 1x3 inch pledgets placed above their cuffs so that each cuff was completely covered. The remaining 6 tracheal tube cuffs (group 2) were unprotected. A Cooper (Santa Clara, CA) 500 Z CO_2 laser was set to 40 W in the continuous mode of operation with a beam diameter of 0.66 mm and was directed at the tracheal tube cuffs until tracheal tube ignition occurred or 1 min had elapsed. There was no ignition of any of the tracheal tube cuffs protected by the saline soaked pledgets after 1 min of 40 watt CO_2 laser fire. Steam was produced by laser application to the pledgets and in some cases a small area of brown thermal decomposition of the pledgets was noted however no flaming occurred. All six tracheal tube cuffs which were not protected by pledgets were ignited in $<$ 1 sec of laser fire and the graduated cylinders were filled with flames and smoke. The incidence of tracheal tube fires was significantly greater in group 2 than group 1 as determined by the Mann Whitney U test ($p < 0.01$).

The laser has enjoyed increasing use in surgery due to its power, precision, hemostatic effects, and decreased incidence of postoperative pain and edema. However, the use of the laser for airway surgery has been associated with catastrophic airway fires.

Metallic foil wrapping of combustible tracheal tubes has been shown to afford effective protection from the laser; however, this technique does not protect the cuff. The present study shows that saline soaked pledgets provide excellent protection of polyvinylchloride tracheal tube cuffs when 40 watts of continuous laser energy was directed at the cuffs. The pledgets can be placed above the tracheal tube cuff by the surgeon before the laser is actuated. They must be kept moist since if they dry, they will become combustible. The pledgets must be carefully retrieved after surgery.

S267

TITLE: AN EVALUATION OF SPECIAL TRACHEAL TUBES WITH THE KTP LASER

AUTHORS: M. Sosis, M.D., Ph.D., B. Braverman, Ph.D., A.D. Ivankovich, M.D.
AFFILIATION: Department of Anesthesiology
Rush-Presbyterian - St. Luke's Medical Center, Chicago, Illinois

The potassium-titanyl-phosphate (KTP) laser is being used increasingly in otolaryngologic surgery of the upper airway including tonsillectomies and resections of subglottic stenosis. In this investigation, we sought to determine the protection offered by special endotracheal tubes manufactured for laser use when the KTP laser was fired at them.

A Laserscope (San Jose, CA) model CE 3924 KTP laser was set to its maximum output of 18 watts in the continuous mode of operation and was propagated through a 400 micron fiber which was directed perpendicularly at the shafts of the tracheal tubes studied. The tracheal tubes had 5 L/min of oxygen flowing through them and were surrounded by air. They rested on wet towels during the study. The four tracheal tubes studied were: 1) a size 7.5 mm ID Mallinckrodt (Argyle, NY) Hi-Lo polyvinylchloride (PVC) tracheal tube; 2) a 7.0 mm ID Xomed (Jacksonville, FL) "Laser Shield" tracheal tube; 3) a 7.0 mm ID Bivona (Hammond, IN) laser tracheal tube; and 4) a 7.0 mm ID Mallinckdrodt "Laser Flex" stainless steel tracheal tube. The laser was actuated until significant combustion occurred or 60 sec had elapsed.

Combustion of the plain PVC tracheal tube started after 14 sec. of laser contact. Flames were noted only at the point of laser impact but thick black smoke was observed to emerge from its distal end. No combusion occurred with the Xomed, Bivona, or Mallinckrodt laser tracheal tubes. However, a small area of damage to the silicone coatings of the Xomed and Bivona tubes was noted at the site of laser impact. The tracheal tubes was not perforated by the laser. A small area of discoloration was seen on the stainless steel shaft of the Mallinckrodt Laser Flex tracheal tube at the site of laser contact but it was otherwise unaffected.

The KTP laser produces radiation at a wavelength of 532 nanometers with a green color. It has a greater tissue penetration than the CO_2 laser and is absorbed by hemoglobin. Thus it has an intrinsic hemostatic action. In contrast with the CO_2 laser, it can be propogated through a fiberoptic bundle. It is being used more and more in laryngologic and other upper airway procedures.

The present study shows that while the Bivona and Xomed laser tracheal tubes provide better airway protection under KTP laser fire than the PVC tracheal tube, they were significantly damaged. A higher laser power, a longer duration of laser contact, or a higher power density (power/area) might perforate these tracheal tubes and cause blowtorch ignition. A higher ambient oxygen concentration might also increase KTP laser damage to these tracheal tubes. The Mallinckrodt stainless steel tracheal tube was not significantly affected by the KTP laser under the conditions of this experiment and is recommended.

S268

Title: **HALOTHANE DOSE RESPONSE CURVES PRE VERSUS POST CARDIO-PULMONARY BY-PASS IN DOGS**

Authors: D.R. Spahn MD, L.R. Smith PhD, R.L. McRae, B.J. Leone MD
Affiliation: Department of Anesthesiology Duke University Medical Center, Durham, NC 27710

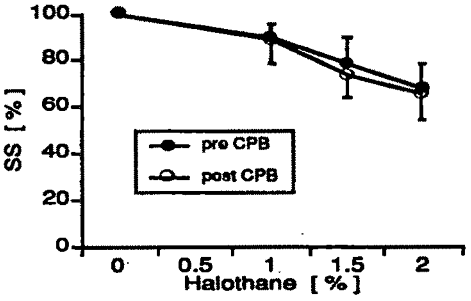
Introduction: Cardio-pulmonary bypass (CPB) with cardioplegia may cause controlled myocardial ischemia with decreased myocardial function [1]. Regional myocardial ischemia causes exaggerated myocardial depression during halothane dose response curves [2]. We hypothesized that asanguineous CPB with a controlled period of cardioplegia would result in ischemic myocardial changes, manifest by exaggerated depression of regional myocardial function during post CPB halothane.

Methods: 9 dogs, receiving humane care according to NIH Publication No. 80-23 (1978), were anesthetized with fentanyl (5 µg/kg iv; 0.1 µg/kg·min) and midazolam (50 µg/kg iv, 1 µg/kg·min). After endotracheal intubation a sternotomy was performed. The heart was isolated, suspended in a pericardial cradle, and instrumented so as to measure left ventricular and central aortic pressure, cardiac output (aortic root Doppler) and regional myocardial function in the left ventricular apex (sonomicrometry). During fentanyl-midazolam infusions, halothane dose response curves (0.0%, 1.0%, 1.5%, 2.0%) were compared pre vs post CPB using asanguineous CPB and hypothermic cardioplegia during aortic cross-clamping (40 min). A multifactorial analysis of variance (complete block design), with least squares means test ($p < 0.05$) was used to compare pre and post CPB halothane dose response curves.

Results: Mean arterial pressure (MAP) (46.4±3.7 vs 85.8±5.9 mmHg [mean±SEM], p<0.01) and hematocrit (19±1 vs 41±2 %, p<0.01) were reduced post CPB. Cardiac output (CO) and systolic shortening (SS) were not affected by CPB. Normalized to fentanyl-midazolam hemodynamics, halothane dose response curves were similar pre and post CPB (see figure). The only differences in halothane effects were 1) CO decreased more post vs pre CPB and 2) systemic vascular resistance did not decrease post CPB as it did pre CPB.

Discussion: The absence of halothane-induced exaggerated regional depression suggests that asanguineous prime CPB with controlled, hypothermic cardioplegia results in no obvious myocardial ischemic dysfunction. The sightly more pronounced decrease in CO post vs pre CPB may indicate reduced cardiac reserves or may be the result of the very low coronary perfusion pressure during the post CPB halothane dose response curves. Lack of halothane effect on systemic vascular resistanc post CPB may represent a homeostatic mechanism to preserve MAP.

References: [1] Wyatt et al., J Thorac Cardiovasc Surgery 97: 771, 1989. [2] Lowenstein et al., Anesthesiology 55:349, 1981.



S269

TITLE: DOES SPHENOPALATINE BLOCK WITH INTRANASAL LIDOCAINE REDUCE ISCHEMIC TOURNIQUET PAIN?

AUTHORS: R.F. Spencer, M.D.; D.G. Silverman, M.D.; T.Z. O'Connor, M.P.H.; L.M. Kitahata, M.D., Ph.D.

AFFILIATION: Anes. Dept., Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

Introduction: Despite many anecdotal reports, it remains uncertain which clinical syndromes actually benefit from sphenopalatine ganglion block (SPGB) and by what mechanism the technique might work, if it works at all. Yang et al. in 1982 documented a statistically significant reduction in ischemic tourniquet pain in healthy male volunteers following intranasal administration of 30 mg of cocaine (10%) compared to saline placebo but did not evaluate lidocaine.[1] In an effort to help clarify the relative efficacy of SPGB with lidocaine and cocaine, the current study was designed to replicate the ischemic tourniquet pain experiment performed by Yang, et al. with the substitution of lidocaine with epinephrine for cocaine.

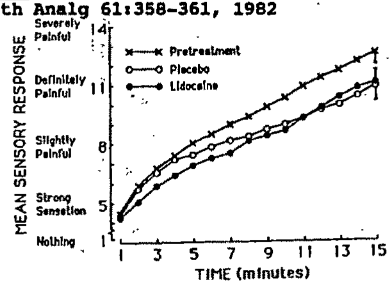
Methods: After IRB approval was obtained, 16 consenting subjects each served as his own control by participating in a series of 2 experimental sessions at the same time of day 1 week apart. Each received a total of 20 mg of intranasal lidocaine with epinephrine at 1 session and saline placebo at the other. This was applied to the vicinity of the SPG by cotton-tipped flexible wire applicators. At each session, the subject had ischemic pain induced in one arm before treatment and the other arm after treatment. He was instructed to squeeze a hand dynamometer to half of his (predetermined) maximum strength for two 10-second periods. Every 10 sec for the following 15 min, the subject indicated his sensory experience. Repeated measures analysis of variance were used to identify at which minutes significant differences among the pretreatment, lidocaine, and placebo groups occurred. Tukey's Multiple Comparisons Test was used to identify which groups were significantly different.

Results: The mean sensory responses averaged over subjects are shown in Fig. 1. While there was a statistically significant reduction in pain following both lidocaine and placebo treatments, there was no evidence of sustained benefit for lidocaine over placebo.

Discussion: Substantial questions remain regarding the efficacy of SPGB and the choice of local anesthetic for it. Currently there is no method to specifically document that the sphenopalatine ganglia have been blocked. Investigations in healthy volunteers have been limited to the tourniquet pain test, which may not be a good model for clinical pain syndromes that would benefit from SPGB. Clearly, further controlled studies, comparing different local anesthetics in patients with various clinical syndromes, are needed to fully assess the benefits and limitations of sphenopalatine ganglion block.

References

1. Anesth Analg 61:358-361, 1982



S270

Title: DIFFERENT ANESTHETIC REGIMENS IN PULMONARY SURGERY

Authors: C. Spies, MD, U. Zaune, MD, G. Boeden, MD, E. Martin, MD

Affiliation: Department of Anesthesia, Klinikum Nürnberg, Nürnberg, W.Germany

Introduction: Pulmonary surgery often requires one-lung ventilation (1LV). During 1LV anesthetics are reported to influence oxygenation (1,2). The purpose of our study was to examine differences between anesthetic regimens before and during 1LV.

Methods: 36 patients, ASA risk group II-III, scheduled for pulmonary surgery, gave their written informed consent to participate in this institutionally approved study. The patients were randomly allocated to one of the following groups: A: Propofol 10 mg kg^{-1} h^{-1}, fentanyl; B: 1 MAC enflurane, fentanyl; C: Thoracic epidural anesthesia, 0.4% enflurane. Ventilation via a double-lumen tube was controlled (FiO_2=1.0, $PaCO_2$ 35-40 mmHg). Measurements were obtained before induction (before epidural block), during two-lung ventilation (2LV), and 20 minutes after starting 1LV. Statistical analysis was performed by the Kruskal-Wallis and Nemenyi test.

Results: Before induction of anesthesia significant differences were not found. During 2LV cardiac index (CI) was significantly decreased in B in comparison with C ($p \leq 0.01$). During 1LV significant differences were not found except for an increased shunt fraction (Qs/Qt) in B (A-B: $p \leq 0.05$; B-C: $p \leq 0.05$; A-C: not significant) (Table 1). During 1LV the lowest PaO_2 measured in each group was 92.4 mmHg in A, 47.1 mmHg in B, and 95.5 mmHg in C, respectively.

Discussion: Since Qs/Qt was significantly increased and hypoxemia occured in B, regimen A or C might be preferred in high-risk patients or where the appliance of CPAP to the nondependent lung is not possible. CI was best maintained in C. Regimen C might be of value in high-risk patients with a poor outcome taking into account possible complications by the epidural block and postoperative reduced need of analgetic agents.

Table 1:		2LV (mean±SD)	1LV (mean±SD)
PaO_2:	A:	424.4±80.0	230.9±103.7
	B:	440.1±64.1	180.0±109.0
	C:	448.4±81.6	240.2±114.3
Qs/Qt:	A:	19.3± 4.8	31.5± 6.6
	B:	21.6±10.9	38.8± 7.2
	C:	17.8± 5.7	32.7± 5.7
CI	A:	2.4± 0.5	3.3± 0.8
	B:	2.3± 0.8	3.5± 1.3
	C:	2.9± 0.5	3.3± 0.6

References:

1.Benumof JL Anesthesiology 67:910, 1987
2.Van Keer L J Clin Anesth 1:284, 1989

S271

TITLE: DESFLURANE VS ISOFLURANE: A COMPARISON OF HEMODYNAMICS IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS

AUTHORS: BD Spiess,M.D., D Jones,D.O., RJ McCarthy,Pharm.D., W Piccione,M.D., E Corey R.N., AD Ivankovich,M.D.
AFFILIATION: Depts. of Anesthesiology/ Cardiovascular Surgery; Rush-Presbyterian-St. Luke's Medical Center; Chicago, IL

Desflurane (I-653) is a fluoridated methyl ethyl ether analog of isoflurane (I). Previous work has shown I-653 to have hemodynamic effects similar to those of I in healthy volunteers. I-653's effects in patients with coronary artery disease (CAD) has not previously been investigated; therefore, the following protocol was performed.

After institutional approval, 40 adult patients undergoing elective coronary artery bypass gave written informed consent. Prior to anesthesia, a PA catheter and arterial line were placed. Hemodynamic data were collected as a baseline before induction; then 1 min after: induction (I_T), laryngoscopy (L_T), incision (S_I), and sternotomy (S_T); just prior to bypass(C_{PB}); 10 minutes after bypass; and at the end of the case. Data collected or calculated included HR, arterial BP, PA and RA pressures, PAOP, CI, SVRI, PVRI, LVSWI, arterial and mixed venous blood gases, and anesthetic concentration. Patients were induced with thiopental 3-4 mg/kg and paralyzed with pancuronium bromide .1 mg/kg. Anesthetic maintenance was randomly assigned to be either I-653 (N=20) or I (N-20) in 100% O_2. The concentration of the inhalation anesthetic agent was adjusted to maintain a surgical plane of anesthesia. Fentanyl up to 10 ug/kg was used as a supplement prior to CPB. Data was analyzed using 2-way ANOVA with repeated measures.

Demographic data showed no difference between groups. Hemodynamic changes from baseline were matched between groups prior to surgical incision. With sternotomy, I-653 patients demonstrated less increase in MAP. There were no post-bypass differences in hemodynamics or outcomes between agents.

I-653 appears to have a similar hemodynamic profile to I in patients with CAD. The differences noted may be explained by I-653's insolubility and rapid titratability. Further work must be done before I-653 can be recommended for patients with CAD.

	I_T	L_T	SI	ST	CBP
I-653					
MAP(mmHg)	87 (17)	100 (20)	91 (21)	90 † (18)	86 (11)
CI(L/min)	2.3 (0.4)	2.6 (1.0)	2.7 (1.3)	2.4 (1.4)	2.4 (1.2)
HR(BPM)	72 (12)	85 (13)	75 (12)	76 (10)	70 (12)
SVRI(UNITS)	1451 (372)	1672 (688)	1482 (488)	1616 (561)	1537 (451)
ISOFLURANE					
MAP(mmHg)	90 (17)	92 (18)	100 (19)	110 † (14)	94 (10)
CI(L/MIN)	2.6 (1.0)	2.4 (0.5)	2.4 (0.6)	2.6 (0.8)	2.3 (0.6)
HR(BPM)	83 (19)	90 (11)	83 (18)	92 (17)	83 (15)
SVRI(UNITS)	1473 (422)	1502 (444)	1649 (513)	1835 (530)	1807 (578)

ALL VALUES MEANS ± SD † = p=0.05

S272

Title: THE EFFECT OF FENTANYL ON THIOPENTAL REQUIREMENTS IN CHILDREN

Authors: WM Splinter, MD, FRCPC
Affiliation: Department of Anaesthesia, Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, Ontario, Canada

Introduction: Fentanyl is a short-acting, potent narcotic commonly administered to children and adults during the perioperative period. In adults, low-dose fentanyl decreases the requirements for general anesthetics.[1] We investigated the effect of fentanyl on thiopental requirements in children during induction of anesthesia.

Methods: With Hospital Ethics Committee approval and parental consent, healthy children, ages 2-12 years undergoing elective surgery, who preferred an IV induction were studied. Patients were excluded if they had respiratory or cardiac disease. The study design and the calculated ED_{50} followed the "up and down method" described by Dixon and used previously in children.[2,3] After establishing appropriate monitoring and IV access, the subjects underwent an IV anesthetic induction. During both phases of the study the subjects were administered a precalculated dose of thiopental as a bolus over approximately 5 seconds into a proximal port of the rapidly flowing IV. In Phase I (induction without fentanyl) the first patient in each subgroup was given 5.0 mg/kg ($10^{0.7}$ mg/kg) of thiopental. Forty-five seconds after injection, the lid reflex was evaluated by gently stroking the eyelashes twice to test for movement of the lid. If the lid reflex was present, the dose for the next patient was increased by 12% ($10^{0.75}$ mg/kg), and if the lid reflex was absent the dose was decreased by 11% ($10^{0.65}$ mg/kg). Six subgroups of patients with a "nominal sample size" of 2 were studied in Phase I. The subjects were studied identically in Phase II, except 3 mcg/kg of fentanyl was administered IV 2 minutes before the lid reflex was tested and the first patient in each subgroup was given 4.0 mg/kg of thiopental ($10^{0.6}$ mg/kg). Data was analyzed using paired and unpaired Student's t test where appropriate, with statistic significance difference assumed when $P<0.05$. Values are listed as mean± SD.

Results: There were 13 patients in Phase I (control group) and 15 subjects in Phase II (fentanyl-treated group). The subjects within each phase were similar with respect to age, weight and gender. The ED_{50} for thiopental was 4.8±0.4 mg/kg for the control group and 3.5±0.2 mg/kg for the fentanyl-treated group, $P<0.0001$.

Discussion: Low-dose fentanyl reduces thiopental requirements for induction of anesthesia in children by 27%. This reduction is similar to that observed in adults.

References: 1. Anesthesiology 1989; 70: 26-30. 2. Anesthesiology 1989; 71: 344-346. 3. Anesthesiology 1983; 59: 421-424.

Phase	Dose of Thiopental mean±SD
Thiopental	4.8±0.4 mg/kg
Thiopental plus Fentanyl	3.5±0.2 mg/kg P < 0.0001

S273

Title: Measurement of End-tidal PCO$_2$ in Infants: Effects of Low Fresh Gas Flows and Volume-cycled Ventilators.

Authors: WM Splinter, MD, FRCPC, LC Torsher, MD

Affiliation: Department of Anaesthesia, Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, Ontario, Canada.

Introduction: Low and high gas sampling aspiration rates, high fresh gas flow (FGF) rates, high respiratory rates, decreased expiratory times, and entrainment of room air into the anaesthetic circuitry are factors which may dilute the expired gas and lead to an imprecise and reduced estimate of ETCO$_2$. In our practice it was observed that the accuracy of ETCO$_2$ was improved by temporarily decreasing FGF, and was not affected by the use of volume-cycled ventilators. This study was designed to assess the effects of low FGF on ETCO$_2$ and the effects of volume-cycled ventilators on ETCO$_2$ measurement in infants ventilated via a coaxial breathing circuit.

Methods: With Hospital Ethics Committee approval and parental consent, we studied 39 elective surgical patients (ages 0 to 24 months). Patients were excluded if they had cardiac or respiratory disease, or if their operation involved the thoracic cavity or the upper abdomen. After induction of anesthesia, the trachea was intubated. The size of the tracheal tube was 19 cm in length and permitted a leak during ventilation between 5 cm water and 30 cm water. Ventilation was controlled with an OHIO 7000 Anesthesia ventilator, Drager Pediatric Anesthesia ventilator or OHIO Pediatric Anesthesia ventilator via a coaxial breathing circuit (CPRAM 13300 Breathing Circuit, Dryden Corporation.) FGF was 1150 ml/min + 100 ml/kg/min, respiratory rate was 20 breaths/min and the initial tidal volume was 15 ml/kg. ETCO$_2$ was measured with a Nellcor N-1000. Sample gas was aspirated via a connector inserted between tracheal tube and the elbow of the coaxial circuit. Ventilator tidal volumes were adjusted to maintain the ETCO$_2$ between 33 and 43 mmHg. Ten minutes after establishing a stable ETCO$_2$, an arterial blood sample was obtained from each patient. Immediately after obtaining the arterial blood sample, the FGF was reduced to 300 ml/min of 100% oxygen for 15 seconds only. ETCO$_2$ was recorded before and after the reduction in FGF. Data was analyzed using unpaired t-tests, paired t-test, linear regression analysis and coefficient of determination (r^2), where appropriate.

Results: Results are displayed in the Table. The Nellcor N-1000 accurately measured ETCO$_2$ in infants whose ventilation was supported by a volume-cycled ventilator via a coaxial circuit (see Table). The accuracy of the monitor was unaffected by the choice of ventilator. The reduction in FGF decreased the accuracy of the monitor.

Discussion: Side-stream capnography using a Nellcor N-1000 is accurate in healthy infants whose ventilation is controlled with a volume-cycled ventilator under normal FGF.

FGF	ΔCO_2 (ABG-ETCO$_2$) pooled data (mmHg±sd)	ΔCO_2 Ohio Ped (mmHg)	ΔCO_2 Ohio 7000 (mmHg)	ΔCO_2 Dräger (mmHg)
high	2 ± 3 r^2 = 0.68	2	2	3
low	-3 ± 4 r^2 = 0.48	-4	-4	-2

S274

Title: EFFECTS OF ENFLURANE AND ISOFLURANE ON CONTRACTILE ACTIVITY OF ISOLATED RABBIT MESENTERIC VEINS

Authors: A Stadnicka, PhD, N Flynn, MB, ZJ Bosnjak, PhD and JP Kampine, MD, PhD

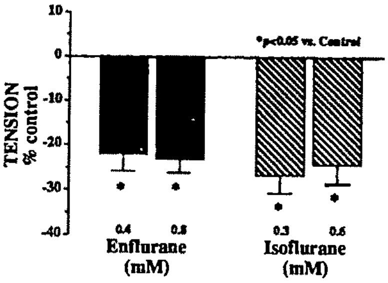
Affiliation: Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI 53226

Recent studies have suggested that volatile anesthetics can induce peripheral vasodilatation by affecting blood vessels responsiveness to sympathetic stimulation.[1,2] The purpose of this study was to examine the direct effect of enflurane (ENF) and isoflurane (ISO) on norepinephrine (NE) induced vasoconstriction in isolated small mesenteric capacitance veins of the rabbit.

After institutional approval, second order branches of mesenteric veins were isolated from the ileum region of 12 thiamylal anesthetized New Zealand white male rabbits (1.5 kg). Three mm long vein segments were suspended in temperature controlled (37°C) jacketed tissue baths containing modified Krebs solution gassed with 95% O_2 and 5% CO_2. Veins were gradually stretched to their optimal resting tension (50 mg) and allowed to equilibrate for 120 min. The vessels were initially constricted with NE (10^{-6}M) as a control. After repeated washout of the baths the veins were again constricted with NE in the presence of either ENF (2.5 and 4.1% equivalent to 0.4 and 0.8 mM ENF in bath solution) or ISO (1.9 and 3.2% equivalent to 0.3 and 0.6 mM ISO, respectively).

Statistical significance of the data was determined by t-test ($p<0.05$).

When compared with the control, ENF and ISO caused significant inhibition of the mesenteric vein constrictions induced by NE (Figure).



In addition, both anesthetics also decreased characteristic rhythmic oscillation and frequency of generated tension . However, none of the above anesthetic effects were dose dependent. Initial investigations indicate that both ENF and ISO also attenuate the constrictions in mesenteric veins induced by endogenous NE released *via* electrical field stimulation. These results indicate that ENF and ISO may induce relaxation of small mesenteric capacitance veins by attenuating their contractile responsiveness to norepinephrine.

References:

1) *Anesthesiology* (In press) 1990
2) *Anesth Analg* 70:530,1990

S275

Title: SUBSTANCE P AFFERENTS MEDIATE CELLULAR AND SYSTEMIC HEMODYNAMIC EFFECTS OF PROPOFOL IN GUINEA PIGS

Authors: W. H. Stapelfeldt, M.D.,
J. H. Szurszewski, Ph.D.
Affiliation: Depts. Anesth., Physiol. & Biophysics
Mayo Clinic, Rochester, MN 55905

Introduction: Propofol (PF) is a new intravenous anesthetic agent of unknown mechanism of action. Previous data suggest that PF does not alter cholinergic transmission in sympathetic ganglia, but may act to specifically increase postsynaptic sensitivity to substance P (SP) (1). The present study was designed to determine the effects of PF on well defined SP-mediated afferent synaptic responses in isolated sympathetic ganglia (2) and on systemic blood pressure of normal guinea pigs and of guinea pigs depleted of SP-containing primary afferents by prior *in vivo* treatment with capsaicin.

Methods: Experiments were performed according to protocols approved by the Institutional Animal Care and Use Committee. Intracellular electrical activity was recorded from sympathetic neurons of the inferior mesenteric ganglion *in vitro* during electrical stimulation of peripheral afferent nerve trunks (2). PF (5 µg/ml) was administered by addition to the Krebs-Ringer buffer superfusate. *In vivo*, systemic hemodynamic changes were measured via a carotid artery catheter in anesthetized (pentobarbital, 50 mg/kg i.p.) guinea pigs in response to PF (1.25 mg/kg) or pentobarbital (PB, 10 mg/kg). Half the animals of each study paradigm were depleted of endogenous SP by prior *in vivo* pretreatment with capsaicin (100 mg/kg).

Results: *In vitro* in normal ganglia, PF increased the amplitude of noncholinergic afferent nerve evoked slow postsynaptic membrane depolarizations (slow EPSPs) by 32% ($p<0.05$) and increased the amplitude of the postsynaptic response to exogenously administered SP similarly by 43% ($p<0.05$). In ganglia obtained from capsaicin-treated animals, slow EPSPs were reduced ($p<0.05$) in amplitude when compared to normal ganglia and were unchanged by addition of PF. Postsynaptic responses to exogenous SP were increased by PF as in normal ganglia (47%,$p<0.05$). *In vivo*, PF in normal animals produced a hypotensive response in 50%, no change in blood pressure in 28%, and a hypertensive response in 22%. In capsaicin-treated animals, PF failed to produce any hypertensive response and evoked only a significantly decreased hypotensive response. PF decreased MAP in normal animals by 20.6 ± 2.2% and in capsaicin-treated animals by 11.3 ± 2.2% ($p<0.05$). The decrease in MAP to PB was similar in both groups of animals (16.4 ± 3.9% vs. 14.6 ± 2.9%, N.S.).

Discussion: These data indicate that systemic hemodynamic effects of PF seen in normal guinea pigs are largely blunted in guinea pigs depleted of SP-containing primary afferents. Taken together with the findings *in vitro*, these data support the hypothesis that PF may act by increasing postsynaptic sensitivity to SP released from primary afferent nerve terminals.

References: (1) Soc.Neurosci.Abstr. 16, 1990, in press
(2) J.Physiol.(Lond.) 411, 1989, 325-345

Supported by NIH DK 17632 and Mayo Foundation.

S276

Title: PERIPHERAL OPIOID RECEPTORS MEDIATING ANTINOCICEPTION IN INFLAMED TISSUE OF THE RAT: EXOGENOUS AND ENDOGENOUS LIGANDS.

Authors: C Stein, MD*, AHS Hassan, PhD, C Gramsch, PhD, K Peter, MD*, A Herz, MD

Affiliation: *Dep. Anesthesiology, Ludwig-Maximilians-University, München, and Dep. Neuropharmacology, Max-Planck-Institut for Psychiatry, Martinsried, FRG

Introduction: Recent evidence indicates that opioids can produce pronounced local antinociceptive effects by activation of peripheral opioid receptors in inflamed tissue (1). This study examined, in a model of unilateral hindpaw inflammation in rats, the antinociceptive effect 1) of systemically (s.c.) administered morphine, 2) of cold water swim (CWS) stress, 3) reversibility of these effects by intraplantar (i.pl.) vs. systemic (s.c.) naloxone (NLX) and 4) the localization of opioid peptides in subcutaneous tissue of the paw by immunohistochemistry.

Methods: This study was institutionally approved. Wistar rats developed unilateral inflammation of the right hindpaw following i.pl. injection of Freund's adjuvant. Four days post inoculation nociceptive thresholds were determined by the paw pressure test. Rats were then given morphine (1.5 mg/kg s.c.) or subjected to CWS for 1 min. In immunocytochemical experiments, sections from both hindpaws were stained with antibodies against ß-endorphin (ß-EP), met-enkephalin (ME) or dynorphin (DYN).

Results: Both morphine and CWS produced marked elevations of paw pressure thresholds in inflamed but not in noninflamed paws. This elevation was dose-dependently and stereospecifically reversible by prior local (i.pl.) but not by s.c. injection of NLX (1-18 µg), indicating the mediation of these antinociceptive effects by local opioid receptors in the paw. Immunocytochemistry revealed the presence of ß-EP and ME containing cells in inflamed but not in noninflamed paws.

Discussion: These findings suggest that both exogenous and endogenous opioid agonists can produce antinociceptive effects by interacting with peripheral opioid receptors in inflamed tissue. Opioid peptides in local inflammatory cells may represent the endogenous ligands for these receptors.

References: J Pharm Exp Ther 248: 1269-1275, 1989.

S277

TITLE: MICROEMBOLI DETECTION IN THE CAROTID ARTERY DURING CARDIAC SURGERY

AUTHORS: CS Stein MS, DA Stump PhD, RA Hager BSEE, AT Rogers MBChB, DS Prough MD, CH Tegeler MD

AFFILIATION: Departments of Anesthesia and Neurology, Wake Forest University Medical Center, Winston-Salem, NC and Carolina Medical Electronics, King, NC

INTRODUCTION: Approximately 300,000 cardiopulmonary bypass (CPB) procedures are performed annually in the USA. Despite continued improvement in the technical aspects of CPB, neurologic sequelae occur in over 50% of cases with frank stroke documented in 2-5% (1,2). Emboli and cerebral hypoperfusion are implicated as the major etiologic factors. Recent reports demonstrate frequent detection of emboli in the middle cerebral artery with the use of bubble oxygenators (3). We report our experience monitoring the carotid artery (CA) for emboli in patients undergoing CPB with membrane oxygenators.

METHODS: After approval of the IRB, we studied 16 patients [8 cardiac valve replacement (CVR), 8 coronary artery bypass grafts (CABG)]. We used a modified Carolina Medical Electronics Dopscan 1060 continuous wave ultrasound device to monitor the left CA throughout surgery. The Doppler signal was evaluated for flow velocity and the high amplitude signature characteristic of microemboli. Anesthesia was managed using a high dose fentanyl/O2 technique. A Sarns 5000 CPB pump and Sarns SMO membrane oxygenator were used. Pre-bypass, the system was flushed through a 0.2 micron Pall filter. During CPB, a 25 micron AF1025C Bentley arterial filter was used. The number and time of embolic events were recorded on magnetic media, and the associated surgical intervention noted. An in vitro model was built to characterize the ultrasound signature generated by emboli of known size. The model consisted of a closed loop of 3/8" Tygon tubing filled with Hespan and Tween 80. The fluid was circulated using a roller pump and known quantities of polystyrene microspheres (50, 90.7, and 193 mu) were injected. The in vivo signals detected were similar to the signals generated in vitro by microspheres >100 micron in size.

RESULTS: CABG patients had an average of 62 ± 25 (median = 66) emboli: 30% when the aortic side clamp was removed, 15% with aortic cannulation and 13% at onset of CPB. CVR patients had an average of 1339 ± 1545 (median = 838) emboli counted with 71% occurring during resumption of cardiac ejection. No emboli were detected in either group while on CPB, during the interval between aortic cross clamping and unclamping.

DISCUSSION: Our results show that emboli are associated with predictable events during cardiac surgery. Aortic cannulation, decannulation, CPB initiation and the resumption of cardiac ejection were accompanied by emboli in both CABG and CVR procedures. In CABG surgery, the removal of the partially occluding side-biting aortic clamp was accompanied by emboli in all cases. CVR generated a much larger bolus of emboli of longer duration with cardiac ejection than did CABG. Few emboli were seen while the aorta was cross clamped, indicating that using a membrane oxygenator plus a filter is sufficient to remove virtually all emboli from the CPB circuit. The total number of emboli detected during CVR was 21 times greater than the number detected during CABG.

REFERENCES:

1. Newman SP. Perfusion 4:93-100, 1989.
2. Stump DA, et al. Anesthesiology 71:A44, 1989.
3. Pugsley W. Perfusion 4:115-122, 1989.

S278

Title: ASSESSMENT OF NEUROMUSCULAR FUNCTION BY 50 HZ TETANY: A COMPARISON WITH TRAIN-OF-FOUR RATIO

Authors: P.E. Stensrud, M.D., K.A. Jones, M.D., E.P. Anderson, B.S., and R.L. Lennon, D.O.

Affiliation: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905

Introduction: A sustained muscle response evoked by 50 Hz 5 s tetany (T50) has been interpreted as evidence of adequate recovery of neuromuscular function. Since a train-of-four (TOF) ratio ≥ 0.75 indicates adequate clinical recovery from neuromuscular blockade,(1) it is hypothesized that if the muscle response evoked by T50 is sustained, the TOF ratio is ≥ 0.75. The purpose of this study was to compare the fade of muscle responses evoked by T50 and TOF during spontaneous recovery from atracurium neuromuscular blockade.

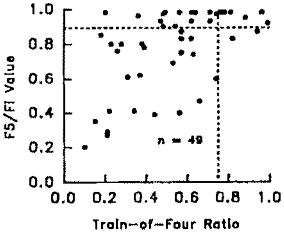
Methods: Following Institutional Review Board approval and informed consent, 9 ASA 1 and 2 adult patients undergoing isoflurane anesthesia for elective orthopedic procedures were studied. The ulnar nerve was supramaximally stimulated at the wrist by a nerve stimulator, and the thumb contractions evoked were measured using mechanomyography. Baseline thumb responses to TOF and T50 were recorded. During spontaneous recovery from atracurium blockade, the thumb contractions evoked by T50 were measured at TOF ratios from 0.1 to 0.98 (n = 49 measurements). The degree of sustained contraction evoked by T50 was expressed as the ratio of the force of contraction at 5 s to the initial force (F5/Fi). An F5/Fi value ≥ 0.90 was considered sustained.

Results: The relationship between the F5/Fi values and the TOF ratios is shown in the figure. When the F5/Fi value was ≥ 0.90, the TOF ratio was < 0.75 for 15 of 23 measurements and < 0.60 for 8 of 23 measurements. This occurred in 5 of the 9 patients studied.

Discussion: The results indicate that a sustained muscle response evoked by T50 did not consistently indicate a TOF ratio ≥ 0.75. When the thumb contractions evoked by T50 are sustained, the TOF ratio may be in the range of 0.20 to 0.74. The relationship between the TOF ratio and clinical recovery from neuromuscular blockade has been previously determined.(1) Our results suggest that a sustained response to 50 Hz tetany may not be a reliable index of recovery, as defined by TOF ratio.

Reference.

1. Anesth Analg 56:55-58, 1977



S279

Title: INSPIRATORY EFFORT (IE) AS A SIGN OF ANESTHETIC DEPTH DURING ISOFLURANE ANESTHESIA

Authors: W.C. Stevens, M.D., R.L. Martin, M.D.
Affiliation: Anes. Dept., Oregon Health Sciences Univ., Portland, OR 97201

We explored whether IE detected from the capnogram or observation is a useful indicator of adequacy of anesthesia which can be correlated with other clinical signs at various alveolar anesthetic concentrations (FA). Since anesthetic requirement depends on the intensity of surgical stimulus (1) and various patient factors (2) and not on FA alone, we attempted to determine if onset or cessation of breathing could be correlated with other clinical signs to help adjust anesthetic dose. METHODS: Methods were approved by our IRB. Sixteen unmedicated and 2 diazepam medicated, 30.3± 6.9 (SD) y.o. ASA I patients were anesthetized with thiopental, 4-6 $mg \cdot kg^{-1}$ and intubated. FA-N_2O 0.5 and sufficient isoflurane (FA-ISO) to achieve a total FA-ANES equal to 1.25 MAC was maintained for 15 min and clinical signs were recorded. We then produced step-wise decreases or increases of FA-ISO until breathing occurred with decreased FA-ISO or breathing stopped with increased FA-ISO and then recorded clinical signs at those times. N-M block, one twitch on train-of-4, was maintained with vecuronium to facilitate surgery and to maintain eucapnia (ET-CO_2 verified by blood analysis). Signs included systolic, diastolic, and mean BP, heart rate, peak airway pressure, pupil position, size and reactivity, tearing, sweating, breath sounds, and swallowing. Data analysis was done by comparing clinical signs during IE or no-IE states (t tests and exact probabilities, signif = $p < 0.05$).

RESULTS: Not all patients made inspiratory efforts when eucapnia was maintained and FA-ANES was at or even well below predicted MAC. There were 63 stepwise decreases and 21 increases in FA-ISO accompanied by 12 instances of onset-of-IE and 10 instances of cessation-of-IE. Nine of 12 onset-of-IE episodes were associated with dec. in FA-ISO and this was significantly related to increase in tearing. IE was associated with three instances of inc. FA-ISO, probably reflecting change of surgical stimulus. All but 1 of 10 IE-to-no-IE episodes, that is cessation of breathing, were associated with inc. of FA-ISO. Diastolic and mean BP dec. significantly in association with cessation-of-IE. ET-CO_2 averaged 35.2± 4.8 (SD) mmHg during IE. All but one ET-CO_2 were < 41 mmHg (51 mmHg). Two patients tolerated dec. in FA-ISO + N_2O to 0.6 MAC without IE, signs of adrenergic response or awareness.

DISCUSSION: IE occurs at eucapnea and with N-M block adequate for abdominal surgery. IE is a reflection of the balance between FA-ISO and intensity of surgical stimulus, that is, adequacy of anesthetic depth. Change of breathing status is an always-available and important sign of anesthetic depth which should be looked for along with all other clinical signs when adjusting FA-ANES.

REFERENCES: 1.Anesthesiol 65:362, 1986. 2.Anesthesiol 53:315, 1980.

S280

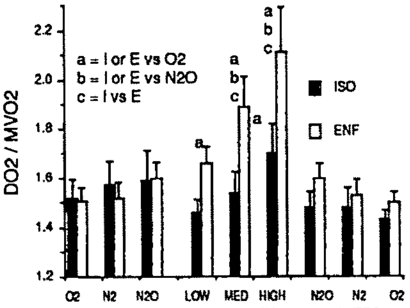
Title: COMPARISON OF N_2O WITH ENFLURANE OR ISOFLURANE ON CONTRACTILITY AND O_2 UTILIZATION IN GUINEA PIG HEARTS

Authors: DF Stowe, MD, PhD, ZJ Bosnjak, PhD
and JP Kampine, MD, PhD
Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

We compared the direct *in vitro* effects of enflurane (E) and isoflurane (I) with N_2O on cardiac mechanics, coronary flow and O_2 utilization using the isolated heart to avoid extrinsic factors.

Methods: Following institutional approval, 32 guinea pig hearts, divided into E (n=16) and I (n=15) groups, were isolated and perfused (55 torr) with Krebs-Ringer solution at 37°C (pH 7.4). Heart rate (HR), atrial-ventricular (AV) time, isovolumetric left ventricular pressure (LVP), +dLVP/dt, mean coronary flow (CF) and coronary inflow and outflow (coronary sinus) O_2 tensions were measured continuously on-line. After control perfusion with 96% O_2 and 4% CO_2, each heart was exposed for 10 min periods to 48% N_2 (in O_2 and 4 %CO_2), to 48% N_2O, to 3 randomized levels of vaporized E (0.8, 1.5, 2.3%) or I (0.5, 1, 1.5%), again to N_2 and N_2O, and finally for 20 min to 96% O_2. Adenosine was injected to test for maximal CF responses. The myocardial O_2 supply to demand ratio (DO_2/MVO_2) was calculated from CF, PO_2a and PO_2v data. Results (means ± SEM) were analyzed by ANOVA and LSD tests; $P < 0.05$ is sig.

Results: HR and AV time were unchanged by N_2 or N_2O; E and I stepwise decreased HR and increased AV time. LVP (control 90±2 torr), and +dLVP/dt, respectively, fell 16±2 and 15±3% with N_2, fell 23±3 and 25±3% with N_2O, fell maximally 48±3 and 44±4% with E plus N_2O, and fell only 28±3 and 26±4% (n.s.) with I plus N_2O. %O_2 extraction was unchanged with N_2 and N_2O and fell maximally 23±4% with E plus N_2O but fell maximally only 6±4% with I plus N_2O. CF increased 92±6% with adenosine, 23±3% with N_2 or N_2O, but not significantly more with E or I. MVO_2 decreased 34±5% with N_2 or N_2O and maximally 52±4% with E plus N_2O, but not significantly more with I plus N_2O. DO_2/MVO_2 ratios with N_2O exposure (figure) were geatly increased by E, but not by I. The increase in DO_2/MVO_2 with E and N_2O was much greater than with I and N_2O, as shown:



Discussion: Our *in vitro* findings show that E depresses the heart more than I in the presence of N_2O, that N_2O, E, and I cause no increase in CF above that of N_2 despite adequate coronary reserve, and that the decrease in O_2 utilization, ie, the increase in the DO_2/MVO_2 ratio, is much more marked by E than by I. These effects are due primarily to reduced O_2 demand rather than to increased O_2 delivery and are more pronounced for E and N_2O than for I and N_2O at equi-MAC concentrations.

S281

Title: CARDIAC EFFECTS OF ETOMIDATE, KETAMINE, MIDAZOLAM, PROPOFOL AND THIOPENTAL ON O_2 SUPPLY AND DEMAND IN GUINEA PIG HEARTS

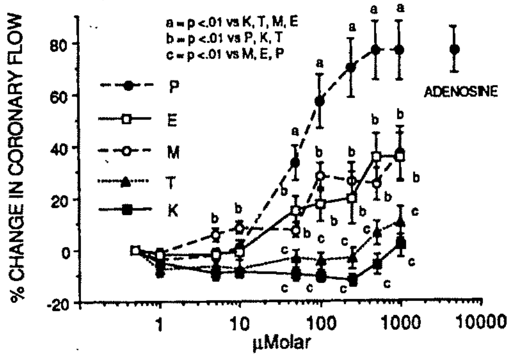
Authors: D.F. Stowe, MD, PhD, D.P. Peller, BS,
Z.J. Bosnjak, PhD, and J.P. Kampine, MD, PhD.

Affiliation: Departments of Anesthesiology and Physiology, The Medical College of Wisconsin, Milwaukee, WI 53226

We conducted a direct dose response comparison of five anesthetic induction agents on mechanical function, coronary flow and O_2 utilization of isolated hearts. These drugs were: etomidate (E), ketamine (K), midazolam (M), propofol (P) and thiopental (T).

After institutional approval, 55 guinea pig hearts were isolated and perfused at constant pressure (55 torr) with Krebs-Ringer solution at 37°C (pH 7.4, 96% O_2, 4% CO_2). Heart rate (HR), atrial-ventricular (AV) time, peak isovolumetric left ventricular pressure (LVP), coronary flow (CF), aortic and coronary sinus pO_2 were monitored continuously. Each heart was perfused stepwise for 10 min with nine increasing levels (0.5 to 5000 µM) of one of the five drugs or its vehicle (11 hearts/drug group). Adenosine was injected before and after each drug study to assess maximal CF reserve. O_2 delivery, DO_2, and O_2 consumption MVO_2, were calculated. Data (means ± SEM) were analyzed by ANOVA and Fisher's means tests. $P < 0.05$ is significance level.

50 to 1000 µM of each agent, caused stepwise decreases in HR, AV time (causing AVB), LVP, and MVO_2. The order of potency for 50% depression of LVP was P=E=M>T>K, a range for P to K of 70 to 370 µM. CF increased maximally with P, as assessed by adenosine (figure). At 100 µM: MVO_2 was unchanged with T and decreased 8±8% with P, 11±3% with K, 15±5% with M and 19±7% with E; DO_2/MVO_2 was unchanged with T and K and increased 52±12% with E, 60±12% with M and 66±7% with P. Compared to T, K, M and E, P caused the greatest increase in DO_2/MVO_2 at the higher concentrations because P caused a relatively greater increase in CF and DO_2 (80%) while the change in MVO_2 (-25±10%) was similar to that of the other drugs (-20 to 39%).



Although increasing equimolar concentrations of each induction agent caused direct cardiac depression, with only a five fold difference in concentrations reducing LVP to the same extent, CF was minimally altered by E and K, moderately increased by T and M, and maximally increased by P. Overall our data suggests that P has moderately greater direct depressant effects on myocardial function but much greater coronary vasodilatory effects than the other induction agents. The lower concentrations of these drugs may attain plasma levels found *in vivo* with induction. Peripheral vascular effects also probably account for the hypotensive effects observed clinically.

S282

TITLE: NEUROPSYCHOLOGICAL DEFICITS AFTER CARDIAC SURGERY

AUTHORS: DA Stump PhD, SP Newman PhD, BT Troost MD, DS Prough MD, C Furberg MD

AFFILIATION: Departments of Anesthesia and Neurology, Wake Forest University Medical Center, Winston-Salem, NC 27103 and Department of Psychiatry, UCMSM, University of London, UK

INTRODUCTION: Research performed in the United Kingdom indicate 75% of patients have neuropsychological (NP) deficits following CABG (1,2). It is unclear if a similar level of NP deficit occurs in the USA (3) because of the wide range in the reported incidence (0-100%). We question if this variance is due to variables such as anesthetic and surgical management or if differences in test selection and statistical analysis affect the outcome calculations (4,5).

Two types of statistical analysis are most common: 1) group comparisons, where the "average performance" is analyzed; and 2) event rate comparisons, where the number of patients with deficits are used to define an "event rate." Often, group comparisons fail to find any statistically significant differences and have tended to be performed in the USA. "Event rate" comparisons report a high incidence of NP deficits and are primarily performed in the UK.

We evaluated both forms of analysis in 51 patients undergoing cardiopulmonary bypass using a series of neuro-psychological tests similar to those used in the UK.

METHODS: After IRB approval and obtaining written informed consent, patients were assessed prior to surgery and 7 days post surgery on 8 NP tests (see Table). A deficit on a NP test was defined as a decline of 25% in performance.

RESULTS: Group analysis showed a significant decline in performance in 4 of 8 tests one week post surgery. Tests requiring sustained fine motor coordination were most impaired. Analysis of individual performance revealed an event rate (an event was a 25% decline on 2 or more tests) of 42%. The inconsistency of the two methods is demonstrated by the results where, despite 41% of the subjects improving on the tapping test, an overall mean decline of only 4.6% was statistically significant.

Table	Group Change pre/post	Subjects/NP Deficits
Trails A	11.7%	25%
Trails B	6.6%	21%
Tapping Dom.	3.6%	13%
Tapping N. Dom	4.6%*	13%
Peg Board Dom.	15.1%*	23%
Peg Board N.	26.5%*	28%
Digit Symbol	10.7%*	25%
Vis. React.Time	0.1% *=p<.05	36%

DISCUSSION: Group analysis has been criticized for being insensitive and failing to discriminate between those patients who deteriorate and those who learn on the neuropsychological tests (4,5). For example, if half of the patients improve and half deteriorate in test performance, the net change could be zero suggesting no problem. These data suggest that both methods should be used to describe this patient population. These results concurs with studies performed in the UK and confirms that patients undergoing routine uncomplicated CABG surgery are at risk for acute neuropsychological disturbance. Test selection may be the most critical factor in characterizing the nature and extent of neurological dysfunction following CABG.

References:

1. Newman S. Cur Psych Res & Reviews 6:115-124, 1987
2. Shaw P, et al. Stroke 18: 700-707, 1987
3. Hammeke et al. J Thor Cardiovasc Surg 96:326,1988
4. Newman SP. Perfusion 4: 93-100, 1989
5. Prough DS, Stump DA, et al. Anesthesiology 1990

S283

TITLE: DOES PRE-CURARIZATION AFFECT POST-OPERATIVE MYALGIA IN CESAREAN SECTION?

AUTHORS: D. V. Subhedar, MD, S.K. Pasricha, MD, K. Shibutani, MD
AFFILIATION: Dept. of Anesthesiology, New York Medical College, Valhalla, NY 10595

Term parturient patients have a very low incidence of fasciculations to intubating dose of succinylcholine[1]. Hence a precurarizing dose of a non-depolarizing agent is often omitted while administering G.A. for cesarean section.

This study was undertaken to see if pre-curarization makes any difference in the incidence of post-operative myalgia (POM). The protocol was approved by our IRB. Fifty-two term parturients undergoing cesarean section under GA were included for the study. Twenty patients randomly selected by the anesthesiologist were given atracurium 4 mg. I.V. followed 4 minutes after by a bolus of 100-120 mg. of succinylcholine for intubation. An independent observer followed the patients post-operatively for 4 days to evaluate for myalgia. All patients were ambulatory 24 hours after surgery.

Of the 32 patients who received no pre-curarization, post-operative myalgia occurred in 14 patients (43%). In the remaining 20 patients who received precurarization, POM occurred in only 2 patients (10%). Furthermore, this myalgia was of a lesser intensity and duration.

Data is represented in the table. Earlier studies have shown that the over-all incidence of fasciculations and POM is low in parturient subjects as compared to the general population.[2,3] Our results indicate that a pre-curarizing dose of atracurium may benefit patients in further decreasing the incidence of post-operative myalgia (10% vs. 43%).

References:
1. Br.J.Anesth. 43,677-80, 1971.
2. Br.J.Anesth. 49,625-28, 1977.
3. Br.J.Anesth. 55,743-45, 1983.

NO PRECURARIZATION		PRECURARIZATION	
32		20	
NO POM	POM	NO POM	POM
18(57%)	14(43%)	18(90%)	2(10%)

S284

TITLE: PATTERNS OF SEDATION AND ANALGESIA IN THE POSTOPERATIVE ICU PATIENT: A SURVEY

AUTHORS: X. Sun MD, T. Quinn MD, & C. Weissman MD
AFFILIATION: Departments of Anesthesiology and Medicine, College of Physicians and Surgeons, Columbia University New York, N.Y.

Critically ill postoperative patients require prolonged sedation and analgesia. To explore drug utilization in these individual, we examined the records from an eight bed tertiary care surgical ICU (patients undergoing cardiac and neuro surgery were excluded). The type and amount of sedative and analgesic drug administered to all the patients during six-month periods in 1986-7 (group A, N = 178) and 1989-90 (group B, N = 270) were recorded. The differences between these two groups were examined using Students' t-test and Chi square analysis.

A majority of patients, 126 in Group A, 144 in Group B were intubated on admission to the ICU. 96% of them received narcotics for sedation. Intravenous fentanyl was used primarily in patients undergoing abdominal surgery. It was given to 71 (56%) Group A and 79 (55%) Group B intubated patients. It was administered as a continuous intravenous infusion 69% of the time in group A and 47% of the time in Group B ($p < 0.05$). The dose in group A, 3.5 ± 1.9(SD) ug/kg/hr (5.5 ± 4.3 mg/d), was significantly higher ($p < 0.05$) than that in group B (2.4 ± 1.4 ug/kg/hr, 3.6 ± 2.6 mg/d). This difference was likely due to the concomitant use of benzodiazepines. Midazolam (3.62 ± 4.3 mg/d) was administered in 74% of the group B patients receiving continuous IV fentanyl while only 30% of the Group A patients ($p < 0.01$) received diazepam (6.9 ± 5.5 mg/d) This reduction in the dose of narcotic was also observed in the intubated patients given intravenous morphine. Those in Group B received 18.1+15.1 mg/day of morphine, those in Group A received 28.1 ± 39.2 mg/d ($p <0.05$). In Group B 47% received midazolam (2.7 ± 2.7 mg/day) while in Group A only 17% received diazepam (6.0 ± 7.2 mg/d).

Another difference between the two groups was a significantly greater use of epidural fentanyl (EPI-FENT) in the non-intubated patients of Group B than Group A (27% vs 4%, $p<0.01$). 81% of the time EPI-FENT was administered by continuous infusion. As a result fewer extubated Group B (44%), than Group A patients (71%, $p < 0.005$), received systemic morphine for analgesia. A smaller total dose of EPI-FENT was used when intermittent boluses (0.57 ± 0.7 mg/day) rather than a continuous infusion (1.25 ± 0.88 mg/day, $p<0.01$) were administered.

The frequency of sedative and analgesic drug administration was assessed hourly for the first 76 hours postoperatively. Peak frequency was achieved between 12 midnight to 4am in both intubated and non-intubated patients. There was also a gradual decrease in medication administration on successive postoperative days. The total medication requirement in the extubated group ranged from 30-70% below that in the intubated group.

This survey demonstrates changes over three years in sedative and analgesic drug use in ICU patients that mirrors changes in anesthetic and pain management practice. Specifically, the increased use of benzdiazepines to reduce the amount of narcotic required to sedate intubated patients and the increased use of epidural narcotics, especially, in patients undergoing thoracic surgery. These results serve as the basis for further study of the efficacy of analgesia and sedation practices.

This study was approved by the Institutional Review Board. Informed consent was not required.

S285

TITLE: PLACEBO, EPHEDRINE, AND ANTIEMETICS IN POSTOPERATIVE NAUSEA AND VOMITING IN AMBULATORY SURGERY PATIENT

AUTHORS: YF SUNG, MD, T. Tillette, CRNA

AFFILIATION: The Emory Clinic, Ambulatory Surgery Center, Atlanta, Georgia, USA.

INTRODUCTION: In the last few years, we have used ephedrine alone or combined it with promethazine i.m., intraoperatively for some patients who have a history of severe nausea/vomiting (N/V), and have obtained very good results. However, not much information has been published on this type of treatment. Therefore, a double-blind study of this treatment was carried out.

METHOD: The study was approved by the Human Investigations Committee. Any patient with a previous history of N/V and in need of general anesthesia with endotracheal intubation was recruited for the study. Induction of anesthesia was accomplished with fentanyl 1 mcg/kg, d-turbocurare 3mg and thiopental 4-5 mg/kg, followed by succinylcholine 1.5mg/kg i.v. for intubation with isoflurane-N_2O-O_2 and muscle relaxants for maintenance of anesthesia. The patients were randomized and assigned to four groups. By the end of the procedure, the patient received i.m.in 1.5cc one of the following four treatments:1. saline (S), 2.ephedrine (E) 25 mg in saline, 3. ephedrine 25 mg plus promethazine 12.5 mg in saline (EP1), 4. ephedrine 25 mg plus promethazine 25 mg(EP2). If the patient had severe N/V in the recovery room, they were treated by standard antiemetics (rescue drugs), i.e., droperidol, metochlopramide, etc. Postoperatively the patient was evaluated by the research nurse during awaking, sitting, prior to discharge, and at 24 hr for N/V and intake of rescue drugs.

RESULTS Sixty-one females ages 20-44 participated. There were significant differences among the 4 groups in incidence of N/V and in use of rescue drugs as shown in the table.

	N/V	Rescue Drugs
S	10/12 (83%)	7/12 (58.3%)
E	7/15 (46.6%)	2/15 (13.3%)
EP1	5/17 (29.4%)	0/17 (0%)
EP2	5/18 (27%)	0/18 (0%)
chi sq test	P=0.015	P< 0.001

There were no statistically significant difference among the groups in time spent in the recovery room.

DISCUSSION Ephedrine particularly in combination with promethazine is effective in minimizing postoperative N/V, even though ephedrine did not completely prevent N/V in all patients. In those patients who did experience N/V, symptoms were mild as evidenced by the fact rescue drugs were rarely required.

S286

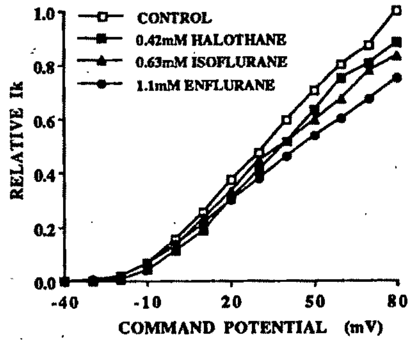
Title: EFFECTS OF HALOTHANE, ISOFLURANE AND ENFLURANE ON K^+ CURRENT IN CANINE CARDIAC PURKINJE CELLS

Authors: Supan F, PhD, N Buljubasic, MD, H Eskinder, PhD, JP Kampine, MD, PhD, and ZJ Bosnjak, PhD
Affiliation: Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI 53226

Potassium channel currents are important in regulating the resting membrane potential as well as the plateau and repolarization phase of the action potential (AP). In cardiac Purkinje fiber, repolarization of the AP is initiated in part by the activation of delayed rectifier K^+ current (I_k)[1] and agents that increase I_k are reported to shorten AP duration.[2] Halothane abbreviates repolarization in false tendon Purkinje fibers of the dog which action may contribute to re-entrant activity.[3] These effects of halothane might be due to blockade of slow sodium current or enhanced I_k. This study examined the effects of halothane, isoflurane and enflurane on I_k in single cardiac Purkinje cells.

After institutional approval, Purkinje fibers from mongrel dog heart were incubated at 37°C for 4 hrs in Ca^{2+} free collagenase solution. The digested fibers were washed and placed in a perfusion chamber containing 1.5 mM Ca-Tyrode solution where the external Na^+ was replaced by N- methyl-D-glutamine (130 mM). Mn^{2+} (2 mM) was added to the external solution to block the inward Ca^{2+} current. K^+ channel current was elicited by depolarizing pulses (200ms) from a holding potential of -40 mV to more positive membrane potentials in 10mV increments. We analyzed the amplitude of I_k before, during and after the introduction of equipotent concentrations of halothane (0.42mM), isoflurane (0.63 mM) and enflurane (1.1 mM).

Figure 1 shows the effect of all three agents on the current-voltage relation of I_k at 194 msec from the beginning of depolarizing pulse on the single cardiac Purkinje cell. Outward current began to appear at -20 mV and reached 1.8 nA at + 80 mV. All three anesthetics, reversibly and significantly depressed the amplitude of I_k in the entire voltage-range studied. At equipotent concentration, halothane, enflurane and isoflurane suppressed the peak I_k by 16±2, 17±1 and 16±1%, respectively.



The results of our experiments indicate that halothane, enflurane and isoflurane suppress the I_k in cardiac Purkinje cells. Reduction of I_k by inhalational anesthetics may counteract the decrease of AP duration[4] produced by depression of slow inward sodium current.

References: 1) *J Physiol* 200:205-231, 1969; 2) *J Gen Physiol* 90:671-701, 1987; 3) *Anesthesiology* 67:619-629, 1987; 4) *Anesthesiology* 7(3A):A521, 1989.

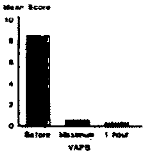
S287

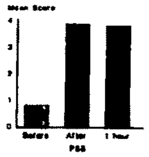
TITLE: **EFFICACY OF INTRATHECAL MEPERIDINE FOR LABOR ANALGESIA**

AUTHORS: C.R. Swayze, M.D., F.G. Sholte, M.D., E.B. Walker, R.N. and J.H. Skerman, D.Sc.
AFFILIATION: Departments of Anesthesiology and Obstetrics and Gynecology, LSUMC School of Medicine in Shreveport, LA 71130-3932

Introduction: Meperidine is an opioid agonist with known weak local anesthetic effects.[1] Our IRB approved prospective study was an endeavor to determine the analgesic efficacy of intrathecal meperidine for labor and delivery.[2,3]
Methods and Materials: After informed consent was obtained, twenty term parturients were given an initial dose of ten mg meperidine intrathecally as one ml via a continuous spinal catheter. Patients scored pain levels (on a Visual Analog Pain Scale) and satisfaction (on a 0 to 4 point scale) before and after the block, and one hour after maximum block was achieved. Motor block was measured hourly during labor. Time to pain relief and return of pain was recorded. A follow-up assessment 24 hours postpartum determined overall patient satisfaction.
Results: Mean VAPS scores ± SEM were 8.57 ± 0.32 before block, 0.62 ± 0.20 after maximum block, and 0.33 ± 0.13 at one hour($p<0.0001$) Mean PS scores ± SEM were 0.83 ± 0.20 before, 3.90 ± 0.07 after, and 3.85 ± 0.08 at one hour. Follow-up satisfaction was "excellent" in 14 of 18 patients, with the remaining four rating it "good". Expulsive efforts were excellent in 14, good in three and fair in one; two patients had cesarean sections. Mean time to onset of pain relief was 3.9 minutes (range 2 - 12 minutes) with analgesia lasting a mean of 83 minutes (range 38 - 180 minutes). Slight motor block was observed in only two patients.
Discussion: The efficacy of intrathecal meperidine is demonstrated by the significant reduction in VAPS and increase in PSS. Pain relief was prompt but duration was highly variable. Slight motor block was infrequent and associated with high dose requirements. Side effects appeared insidiously. Although efficacy is demonstrated, the usefulness of the technique is limited by a significant tachyphylaxis associated with blocks that were required for more than a few hours.

References:
1. Anesth Analg 70:658, 1990
2. Anesth Analg 66:235, 1987
3. Br J Anaesth 58:1012, 1986





S288

TITLE: PREOXYGENATION TIME - INFLUENCE OF ANTHROPOMETRIC AND PULMONARY VARIABLES?

AUTHORS: T.Symreng,M.D.,Ph.D.,M.P.Mehta,M.D., J.S.T.Sum-Ping,M.D.,E.F.Wade, R.D.
AFFILIATION: Department of Anesthesia, University of Iowa College of Medicine, Iowa City, IA 52242

Introduction: Anesthetic induction in surgical emergencies and cesarean section are performed with preoxygenation. We investigated the relationship between anthropometric and pulmonary variables and preoxygenation time.
Methods: With informed consent and approval from the University of Iowa Human Research Committee, nine volunteers underwent an anthropometric assessment (weight, age, height, skin folds of biceps, triceps, subscapula and suprailiac region) and from these data body density(D), fat mass(FM) and fat free mass(FFM) were calculated(1). After pulmonary function tests (FVC, FEV_1, PEF and FEF_{25-75}) were performed (Respiradyne II), each volunteer was asked to breathe through a mouthpiece connected to an oxygen primed circle system in two separate sessions with 5 and 10 L/min oxygen flow, respectively. Inspired and expired gas was analyzed with a mass spectrometer (Ohmeda multi-gas analyzer 6000) and time for nitrogen to reach 5% were recorded. The relationship between time to 5% expired nitrogen at the two oxygen flow rate and anthropometric and respiratory variables was evaluated with linear regression and paired t-test. $P<0.05$ was considered significant.
Results:
Denitrogenation

O2-flow, L/min	FVC	FEV	PEF	FEF	Age
5	0.14	-0.21	-0.06	-0.32	0.79**
10	0.09	-0.02	0.17	-0.16	0.06

	Wt.	Ht.	BSA	D	FM	FFM
5	0.24	0.63*	0.51	-0.64*	0.51	-0.27
10	-0.43	0.54	-0.17	0.17	-0.28	-0.55

Age ($p<0.01$) and height ($p<0.05$) correlated positively and density negatively($p<0.05$) with time to 5% nitrogen at 5 L/min oxygen flow, but not at 10 L/min flow. None of the other anthropometric and respitory variables correlated significantly with time to 5% expired nitrogen. Time to 5% nitrogen was shorter ($p<0.001$) at 10 L/min flow, 115±35 sec, compared to 5 L/min, 316±43 sec (mean±SD).
Discussion: The relationship between age and washout of nitrogen could be due to an increasing closing volume or decreased metabolic rate. In healthy volunteers higher oxygen flow rates outweigh the influence of anthropometric and pulmonary variables on denitrogenation time.
Conclusion: Preoxygenation in healthy individuals is most efficient when high oxygen flow (10 L/min) is used and anthropometric and pulmonary variables are less important. When lower flow (5 L/min) is used increasing age and height prolong the time needed for denitrogenation.

Reference: Durnin JVG et al. Br J Nutr 1974;32:77.

S289

Title: ASSESSMENT OF MYOCARDIAL PERFUSION IN PATIENTS WITH SUBARACHNOID HEMORRHAGE AND AN ABNORMAL ECG

Authors: M.D. Szabo, M.D.; G. Crosby, M.D.; W.E. Hurford, M.D.; W.H. Strauss, M.D.
Affiliation: Departments of Anesthesia and Radiology, Massachusetts General Hospital, Boston MA 02114.

New ECG abnormalities are common in patients with subarachnoid hemorrhage (SAH)[1] but their clinical significance is uncertain. The ECG changes are often attributed to the CNS event and are disregarded even though they resemble changes of myocardial ischemia and some data[2-4] support an ischemic mechanism. Myocardial perfusion has not been examined directly in such patients, however. The purpose of this study, therefore, was to assess the relationship between ECG abnormalities and myocardial ischemia, as evaluated by thallium scanning, in patients with SAH.

Myocardial perfusion was evaluated prospectively with thallium-201 scintigraphy in 13 patients with an abnormal ECG associated with a recent SAH. Scans were performed either as part of an institutionally-approved study protocol and with informed consent or as part of the routine clinical evaluation of an abnormal ECG. Three views of the heart were obtained and comparable reperfusion images were obtained 2-3 h later. Each scan was read by both a cardiologist and a radiologist blinded to the ECG abnormality and neurological condition of the patient. A 12-lead ECG was obtained on the day of the scan and data as to cardiac risk factors, pre-existing heart disease, neurological grade, time since SAH, and electrolytes were also documented.

Patients (57 ± 12 y) were scanned 3 ± 2 days post-SAH. Ten had T wave inversions and 3 had minor ECG changes. Three patients had ischemia diagnosed on thallium scan; 1 had pre-existing heart disease and 2 had a risk factor. Two of 7 grade III/IV and 1 of 6 grade I/II patients had a positive scan. One of 3 patients who died had a positive scan.

These results indicate there is no consistent relationship between an abnormal ECG and myocardial ischemia, as determined by thallium scanning, in patients with SAH. Nevertheless, since ischemia was present in several patients but could not be reliably predicted by history, severity of ECG change, or neurological grade, the possibility of underlying myocardial ischemia should be considered seriously in any patient with an abnormal ECG following SAH.

References
1. Stroke 18: 558, 1987.
2. Br Heart J 40: 802, 1978.
3. J Am Coll Cardiol 12: 600, 1988
4. J Neurosurg Anesthesiol 2: S-16, 1990.

S290

Title: PHARMACOKINETICS,ONSET AND DURATION OF ACTION OF ORG 9426 IN HUMANS: NORMAL *VS.* ABSENT RENAL FUNCTION.

Authors:J Szenohradszky MD, V Segredo MD, JE Caldwell MBChB, M Sharma PhD, LD Gruenke PhD, RD Miller MD.
Affiliation: Department of Anesthesia, University of California, San Francisco, CA 94143-0648.

Introduction: ORG 9426 is a new steroidal monoquaternary nondepolarizing neuromuscular blocking drug. Both animal (1) and human studies (2,3) have shown that it has a shorter time of onset and shorter or similar duration of action when compared with vecuronium. It is free of cardiovascular effects. This study investigates the effect of renal failure on the pharmacokinetics and the onset and duration of action of ORG 9426.

Methods: Following approval by our Committee for Human Research 10 patients with normal renal function, ASA class 1 or 2, scheduled for elective surgery, and 10 with end-stage renal disease, ASA class 3, scheduled for cadaver kidney transplantation were studied. Informed written consent was obtained from all patients. Anesthesia was induced with thiopental, 1-4 mg/kg iv, and maintained with isoflurane, 0.4-1.0 %, and nitrous oxide, 60-70%,(end-tidal concentrations). Supramaximal stimuli of 0.2 msec duration in a train-of-four sequence (2Hz) were delivered every 12 seconds, *via* needle electrodes, to the ulnar nerve at the wrist. The mechanically evoked response of the adductor pollicis muscle to the first stimulus in each train (T_1) was measured. ORG 9426, 0.6 mg/kg,(2.5 x ED_{90}) was injected rapidly iv and venous blood samples were drawn at intervals for 240 min thereafter. The times from injection of ORG 9426 until complete ablation of T_1 (onset) and until the T_1 returned to 25% of control (duration) were recorded. Plasma concentrations of ORG 9426 were measured by capillary gas chromatography. Data were analyzed by non-linear regression and described by a three compartment model. Statistical comparisons were by Mann-Whitney U test.

Results: ORG 9426 had a rapid onset of action, complete neuromuscular blockade being produced in less than 90 sec in all except two patients.There were no significant differences in any variable between patients with normal or absent renal function (see table).

	n	Normal Function	n	Renal Failure
Onset (sec)	10	75 ± 40	9	62 ± 18
Duration (min)	10	47 ± 12	10	49 ± 26
V_{cent} (ml/kg)	6	56 ± 21	5	62 ± 27
V_{ss} (ml/kg)	6	283 ± 183	5	310 ± 179
$t_{1/2\beta}$ (min)	6	203 ± 169	5	112 ± 79
Cl (ml/kg/min)	6	2.8 ± 0.9	5	4.6 ± 4.0

All results are mean ± SD.

Discussion: We conclude that renal failure has no influence on the onset, duration of action or pharmacokinetics of this large bolus dose (2.5 x ED_{90}) of ORG 9426. The onset of ORG 9426 appears to be more rapid than any other non-depolarizing neuromuscular blocking drug currently available.

References: 1.Brady-KK et al.: Anesthesiology 72:669-674,1990. 2. Wierda JMKH et al.: Br.J. Anesth.64:521-523,1990. 3. Nagashima H et al.: Anesthesiology 71: A773,1989.

S291

Title: Anesthesia And Upper Respiratory Infections: The Effect Of Tracheal Intubation
Authors: A.R. Tait, PhD, P.R. Knight, MD, PhD
Affiliation: Dept. of Anesthesiology, Univ. Michigan
Medical Center, Ann Arbor, MI 48109

Introduction. The decision to proceed with anesthesia for the patient who presents with an acute upper respiratory infection (URI) remains controversial, particularly if the patient requires tracheal intubation. This report presents preliminary data from an ongoing prospective study designed to determine the effects of anesthesia on patients who present with acute URIs for procedures requiring tracheal intubation.

Methods. The study population (with informed consent and approval from our Institutional Review Committee) consisted of children between the ages of 1 and 16 years who were evaluated at the Ophthalmology or Urology clinics. Children were randomly allocated to a control or surgery group. The control group (n=50) was evaluated over a three week period following the initial clinic visit (prior to anesthesia) and the surgery group (n=65) was evaluated for three weeks following anesthesia and surgery for strabismus or hypospadias repair. Children were classified as having an URI if they met certain predetermined criteria. Based on these criteria, the control and surgery groups were subdivided in three smaller groups. Group I - symptomatic children fulfilling the URI criteria. Group II - symptomatic children who did not fulfill all the URI criteria or who had a history of an URI in the two weeks preceding surgery. Group III - asymptomatic children. Prior to surgery all surgery group children were evaluated for fitness to undergo the procedure. All surgery children had a standard anesthetic of halothane/O_2/N_2O. All had their tracheas intubated. Information on the children's health in the three week follow-up periods was by standardized questionnaire.

Results. The control and surgery groups and their subgroups were well matched for age, sex, race, and socioeconomic status. The incidence of perioperative respiratory complications was similar for each of the three surgery groups. The incidence of laryngospasm in the symptomatic Group I was 11.1% compared to 5.9%, and 13.3% in Group II and III, respectively.

The mean duration of anesthesia and surgery was 96 min., and 59 min., respectively. These times were similar for each individual group. The incidence rates for congestion, productive and nonproductive cough in the three week follow-up periods were less for the surgery group than the control group, however, these differences did not achieve significance. All other symptoms were similar between the two groups. There were no cases of postoperative pneumonia nor other serious sequelae.

Discussion. Preliminary results from this study suggest that children who present for anesthesia requiring tracheal intubation with acute, uncomplicated URIs do not have an increased incidence of perioperative complications nor an exacerbated postoperative course. It is hoped that results from this study, albeit preliminary, will help the anesthesiologist in predicting the outcomes of anesthesia for the patient with an acute URI.

S292

Title: EPIDURAL ANESTHESIA AND ANALGESIA IS SAFE FOR PATIENTS WITH ASTHMA - A SURVEY OF 383 PATIENTS
Authors: K.Tanaka,M.D.,S.Shono,M.D.,
R.Watanabe,M.D. and K.Dan,M.D.
Affiliations: Dept. of Anesthesiol. School of Med.
Fukuoka University
Fukuoka, JAPAN 814-01

Introduction. Choice of anesthesia in asthmatic patients is controversial. Authors recommend regional anesthesia when feasible(1). However, regional anesthesia such as high spinal or epidural block involves sympathetic nerves, which may trigger asthmatic attack. Bromage reported marked improvement of status asthmaticus by epidural blockade(2). Our experience with surgical asthmatic patients is reported here.

Method. Preoperative patients with asthma were carefully evaluated. They were classified into three groups according to Kingston & Hirshman(1). Following informed consent, epidural anesthesia and analgesia (EAA) was planned, unless otherwise contraindicated. Anesthesia was maintained with epidural analgesia, intravenous sedatives and analgesics but without endotracheal intubation whenever possible. Postoperatively, medical charts were closely reviewed for asthmatic attacks and medications.

Results. Excluding thoracotomy patients, there were 383 asthmatics in 16074 patients who underwent surgery under EAA. Fourteen patients(3.7%) developed mild asthmatic attacks which were treated with aminophylline(13), steroids(8), and/or halothane(1). There were no patients who developed into status asthmaticus, refractory bronchospasm or cardiac arrest. Two hundred and seventy seven patients belonged to Group 1, 64 to Group 2 and 42 to Group 3, and 9(3.2%), 1(1.6%) and 4(9.5%) developed asthmatic attacks, respectively. Incidence of asthmatic attacks according to the site of epidural puncture and presence or absence of endotracheal tube are summarized(Table 1). No statistical significant difference was seen.

Table 1. Incidence of Asthmatic Attacks Under Epidural Anesthesia and Analgesia

Site of Epidural Puncture	$>T_{12}$	$T_{12}>$	Total(%)
No Intubation	4/125(3.2)	6/219(2.7)	10/344(2.9)
Intubation	3/26(11.5)	1/13(7.7)	4/39(10.2)
Total	7/151(4.6)	7/232(3.0)	14/383(3.7)

Discussion. In asthmatic patients, careful preoperative assessment, selection of premedicants, anesthetics and anesthetic method are mandatory. In our series of patients, EAA was encountered with low incidence of mild asthmatic attacks which were easily controllable without extraordinary measures. Thus, EAA is safely recommended for most of the asthmatic patients.

References. 1.Anesth Analg 63:844-55,1984
2.Epidural Analgesia. Philedelphia, WB Saunders,1978, pp.638-643

S293

TITLE: USE OF MIDAZOLAM IN COMBINATION WITH PROPOFOL FOR SEDATION DURING MAC

AUTHORS: E. Taylor, M.D., P.F. White, Ph.D., M.D.
AFFILIATION: Department of Anesthesiology, Washington University, St. Louis, MO 63110

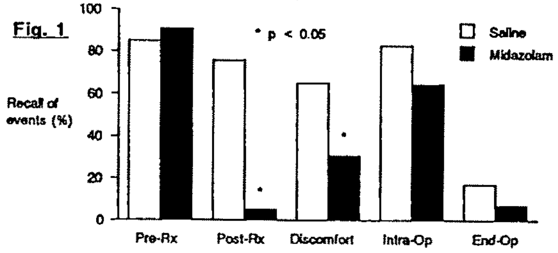
Propofol infusion can be used to produce sedation during local and regional anesthesia. Its primary advantage over other sedative drugs relates to a rapid recovery profile. In contrast to midazolam, however, pain on injection and intraoperative recall are frequently reported at subhypnotic levels of propofol. We designed a randomized, double-blind, placebo-controlled study to evaluate the perioperative effects of midazolam when given prior to propofol for sedation during monitored anesthesia care (MAC).

42 healthy, consenting adults undergoing minor outpatient operations under local anesthesia were assigned to receive either midazolam (M), 2-3 mg iv, or saline (S), 2-3 ml, for premedication according to an IRB-approved protocol. All patients received a propofol infusion, 25-120 ug/kg/min, using a Bard InfusOR pump to maintain a stable level of sedation during the procedure. Prior to administering the study medication, patients were shown a picture and asked to assess their anxiety and sedation levels using linear analog scales (0 mm = minimal to 100 mm = maximal). These assessments were repeated 5 min after injection of the study drug at the time we initiated the propofol infusion at 75 ug/kg/min. At the end of the procedure, the patients were shown a third picture. Upon discharge from the outpatient unit, patients were asked to complete a short questionnaire evaluating their perioperative experience. Data were analyzed using ANOVA and Chi-square tests, with $p<0.05$ considered significant (mean values ± S.D.).

The two groups were similar demographically [age: 42±15(S) vs 41 ± 16 (M) yr; weight: 75±16 vs 67±14 kg; duration of procedure: 61±27 vs 51±26 min]. Midazolam produced a significantly greater increase in sedation level (9±11 to 44±28 vs 7±9 to 29±21 mm) and decrease in anxiety level (55±27 to 29±21 vs 53±26 to 46±28 mm). In addition, midazolam decreased recall of the post-treatment picture and propofol-induced pain on injection (fig. 1). The propofol dosage requirement was similar in the two treatment groups [65 ± 18 vs 71 ± 20 ug/kg/min] and there were no differences in cardiorespiratory variables. Finally, midazolam did not significantly prolong times to ambulation (57±28 vs 53±34 min) or discharge (88±39 vs 77±41 min).

In summary, these data would suggest that midazolam, 2-3 mg iv, produces increased sedation, amnesia and anxiolysis when administered prior to propofol infusion without prolonging recovery after minor outpatient procedures.

Fig. 1



S294

TITLE: DILTIAZEM VS NITROPRUSSIDE: DETECTION OF POST-CABG ISCHEMIA USING PRESSURE-VOLUME LOOPS

Authors: Teasdale S , Boylan J,Karski J, Ivanov J, Young P, Weisel R

Affiliation: Departments of Anaesthesia and Cardiovascular Surgery, Toronto General Hospital, Toronto, Canada M5G 2C4.

Introduction: Optimal therapy of post-CABG hypertension (HT) is unclear. Sodium nitroprusside (SNP) may cause anaerobic myocardial metabolism by reduced perfusion pressure or steal mechanisms[1]. Calcium antagonists such as diltiazem (DTZ) may enhance metabolic reserve[2]. Left ventricular (LV) pressure-volume (P-V) relationships are sensitive indices of pump function and diastolic compliance. We examined the effects of SNP and DTZ on post-CABG systolic and diastolic function.

Patients and Methods: With institutional approval and patient consent, 42 elective CABG patients developing postoperative HT, defined as a mean arterial pressure (MAP) >95 mmHg, were randomized to receive intravenously either DTZ or SNP, titrated to an MAP of 90 mmHg. Standard hemodynamic indices were measured during normotension (NT), HT and therapy. Direct LV pressures were recorded and LV end-diastolic and end-systolic volumes (EDVI/ESVI) calculated using radionuclide ventriculography. LV end-systolic elastance (E_{es}) and modulus of diastolic chamber stiffness (Kp) were calculated.

Results: Both agents reduced systemic vascular resistance and maintained cardiac output. Heart rate decreased with DTZ and increased with SNP. Pulmonary capillary wedge pressure (PCWP) decreased with SNP. E_{es} and Kp increased from NT to HT. DTZ reduced both E_{es} and Kp relative to HT values. SNP maintained E_{es} at HT levels and increased Kp relative to NT and HT.

Discussion: Treatment of post-CABG HT with SNP was associated with impaired LV diastolic function, consistent with previous evidence of anaerobic myocardial metabolism[1,2]. DTZ enhanced diastolic compliance. These effects were not previously detectable by simple calculation of the PCWP-EDVI relationship[2].

Conclusions: DTZ therapy of post CABG HT provided better myocardial protection than SNP. LV P-V loop data is a more sensitive detector of myocardial ischemia than static PCWP-EDVI relationships.

References:

1. J Thorac Cardiovasc Surg 86: 47-56, 1983
2. J Thorac Cardiovasc Surg 96: 122-32,1988.

S295

Title: PATIENT ACCEPTANCE OF INTERSCALENE BLOCK

Authors: **J. E. Tetzlaff, M.D.**, C. Spevak, M.D., H. Yoon, M.D., J. Brems, M.D.

Affiliation: Departments of General Anesthesia and Orthopedic Surgery, Cleveland Clinic Foundation, Cleveland, Ohio

INTRODUCTION: There have been no studies assessing patient satisfaction with the interscalene brachial plexus block in patients undergoing shoulder surgery. However, there have been scattered reports of patient satisfaction with other types of regional techniques[1-5]. To better understand patient acceptance, comfort, and post-op pain control, we retrospectively surveyed 25 patients who previously underwent general anesthesia and were now having regional anesthesia.

METHODS: 25 patients were interviewed 24 hours after shoulder surgery under interscalene block. Each had prior shoulder surgery under general anesthesia within 3 years. 13 questions were asked and data collected. Results were analyzed with chi-squared test. Significance was considered to be $p < 0.05$.

RESULTS: Of the 25 patients surveyed, 24 preferred the interscalene block. Several other variables were statistically significant. Tolerance of the block and being awake during surgery were acceptable to the patients (25/25, 23/25). Only two patients complained of excessive pain during the block. The interscalene group had better pain control and less nausea and vomitting. The adequacy of pre-operative evaluation and premedication between the groups did not appear to influence outcome. The data is summarized in Table 1.

DISCUSSION: Patients who previously underwent general anesthesia for shoulder surgery and subsequently received an interscalene block preferred the interscalene block. This study only addressed the patients' perception of their experience, as no quantitative data was obtained. To our knowledge, this is the only study which addresses patient satisfaction of the interscalene block. With patient satisfaction increasingly becoming an issue, both anesthesiologists and surgeons must become aware of patients' acceptance of regional techniques.

REFERENCES:

1. Obstet Gynecol 70:560-3, 1987
2. Am J. Surg 153:560-3, 19 (?)
3. J R Coll Surg. Edinb 28:14-6, 1983
4. Am J Surg 42:355-7, 1976
5. Plast. Reconstr Surg 65:39-41, 1980

Table 1

	General Anesthesia	Block
Adequate premed	20/25	23/25
Adequate pre/op	22/25	24/25
Excessive pain during block		0/25
Upset awake		2/25
Adequate sedation		23/25
Good immediate analgesia	6/25	25/25*
Recovery Analgesia better	0	21*
Nausea	17	2*
Vomiting	13	2*
Early Ambulation	2	14
Overall preference	1	24*

* Significant difference ($p < 0.05$)

S296

Title: AUTOMATED ANESTHESIA RECORDS: ARE THEY BETTER?

Author: D. N. Thrush, M.D.

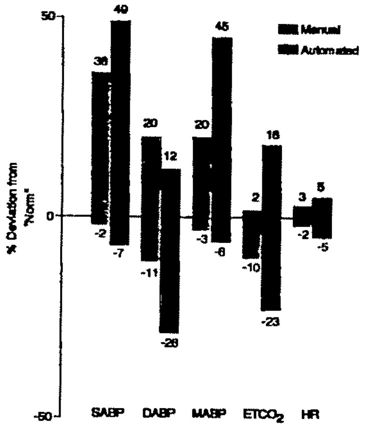
Affiliation: Department of Anesthesiology, University of South Florida College of Medicine, Tampa, FL 33612

Introduction: During anesthesia, accurate and timely charting of vital signs is medically and legally essential, but difficult. Automated patient information management systems reportedly produce more accurate, complete, and contemporaneous records with fewer distractions than the classic manually produced anesthesia records. Such records are used often for retrospective review of appropriateness of anesthetic management. Therefore, accurate recording of information is essential. We wished to determine whether the information recorded automatically was significantly different from manually recorded data.

Methods: Records of one neurosurgical, one general surgical, and eleven open heart cases from the initial one and a half hours of general anesthesia were studied. The cardiac records from the prebypass period only were reviewed. Blood pressure, pulse, end-tidal carbon dioxide tension, and oxygen saturation were measured with standard automated methodology. Results were displayed and recorded manually by the clinician and by an automatic recording device (Arkive, Diatek). Artifact noted on the automated record was not included in the data analysis. Clinically acceptable ranges of normal values for all variables were determined as follows: systolic blood pressure (SABP), 90-120 mmHg; diastolic blood pressure (DABP), 50-70 mmHg; mean blood pressure (MABP), 60-80 mmHg; heart rate, 50-90 bpm; end-tidal carbon dioxide tension ($ETCO_2$), 30-40 mmHg; and O_2 saturation 90% to 100%. We calculated the frequency that these variables exceeded the predetermined norms. To determine the statistical significance of differences in variables recorded manually and automatically, a non-parametric analysis was performed.

Results: We found that manually recorded records consistently minimized abnormalities in vital signs with the exception of DABP (Figure). Oxygen saturation was observed to be less than 90% on two occasions on the automated record, but never when recorded manually.

Conclusion: In complex operations such as open heart surgery with as many as 20 different vital signs noted every 15 min, recording of data may detract from patient care. Moreover, results indicate that the automated system documented more variables that exceeded acceptable normal values. Since the automated record keeper documented physiologic status more accurately than the classic manual method, it appears to be the preferable method for recording vital signs during anesthesia.



S297

Title: PREMEDICATION IN PRE-SCHOOL CHILDREN WITH ORAL, RECTAL AND NASAL MIDAZOLAM

Authors: W. Tolksdorf, M.D. Ph.D.; Ch. Eick; M. Amberger.

Affiliation: Clinic of Anesthesiology, RWTH Univ. of Technology, Aachen FRG

Aim of the investigation:
Midazolam is often used for the premedication of children in the critical pre-school age. Different noninvasive routes of administration have been described. In a prospective study we compared the effects of oral, rectal and nasal Midazolam in commonly used dosages.

Patients and Methods:
90 children, undergoing surgery in general anesthesia were assigned to oral (0,4 mg/kg) Midazolam (MO), rectal (0,5 mg/kg) Midazolam (MR) or nasal (0,2 mg/kg) Midazolam (MN), according to the child's and/or parent's preferred route of administration, after having obtained the parent's informed consent. It was applied on the ward before the transport to the operation theatre. The following parameters were assessed by the observer and the anesthesiologist at different times: Sedation, acceptance (child, anesthesiologist), mood, emotion, defense, pain, nausea and vomiting, heart and respiratory rate. Statistics: Wilcoxon Test ($p \leq 0,05$).

Results:
All groups were comparable with respect to age, weight and type of surgery. There was no difference in the anesthesiologist's acceptance of the premedication. The children accepted the oral route best compared to MN ($p \leq 0,05$) and MR (n.s.). The fastest onset of action was found after MR. After MN many children became euphoric ($p \leq 0,05$). The effect of MO was good in many children, but less predictable. MO children experienced more nausea and vomiting ($p \leq 0,05$) in the postoperative period and were more sedated compared to MO and MR. There was no differences in the physiological parameters.

Discussion and conclusions:
The results can be explained by the different characteristics of absorption and patient's acceptance. The choice of the route of administration according to the child's or parent's opinion can be recommended but does not guarantee success. MR has the fastest onset of action, MO is accepted best, MN worst. MO produces more side effects than MN and MR, especially in the postoperative period. If the child accepts the rectal route of drug administration this should be preferred because of a high success and low side effect route.

S298

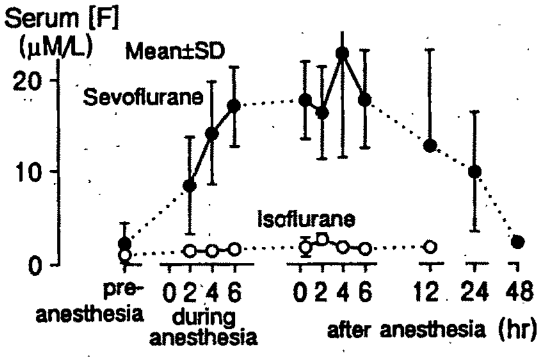
Title: EFFECT OF PROLONGED ANESTHESIA WITH SEVOFLURANE VS ISOFLURANE ON SERUM FLUORIDE IN SURGICAL PATIENTS

Authors: K Toriumi MD, Y Tanifuji MD, N Yasuda MD, K Kobayashi MD,

Affiliation: Dept of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan

Introduction: Sevoflurane is metabolized resulting in an increase in serum inorganic fluoride concentration ([F]) (1), which is lower than the [F] that renal failure may occur (2). Prolonged administration of sevoflurane may allow a greater amount of sevoflurane to be metabolized by producing greater tissue stores of sevoflurane, and this may result in a higher concentration of and/or an extended period of increase in serum [F]. In this study, effects on serum [F] of prolonged administration of sevoflurane and isoflurane were investigated in surgical patients.
Methods: With institutional approval and informed consent, 7 adult patients scheduled for more than 8 hr of surgery were randomly anesthetized with sevoflurane (N=4) or isoflurane (N=3). Serum [F] was measured before and 2, 4, 6 hr after the start of administration, and 0.5, 2, 4, 6, 24, 48 hr after the administration of the volatile anesthetic was discontinued.
Results: Sevoflurane and isoflurane total doses were 8±3 MAC-hours (mean±SD) and 15±3 MAC-hours, and durations of administration were 9±1 hr and 11±2 hr, respectively. Serum [F] increased when sevoflurane was administered and returned to pre-anesthesia values at 48 hr after discontinuation, but [F] did not increase when isoflurane was administered (Figure).
Discussion: The results suggest that sevoflurane may not be the optimal choice for prolonged anesthesia.

References:
1. Holaday DA, et al.. Anesthesiology 1981;54:100-6.
2. Cousins MJ, et al.. JAMA 1973;225:1611-6.



S299

Title: COGNITIVE RECOVERY FROM 0.65 MAC DESFLURANE OR ISOFLURANE ANESTHESIA WITH 60% NITROUS OXIDE

Authors: S.K. Tsai, M.D., C. Lee, M.D., W-F Kwan, M.D., B-J Chen, M.D., E. Cantley, R.N.
Affiliation: Dept. of Anesthesiology, Harbor-UCLA Medical Center, Torrance, CA 90509

Desflurane (DF) has lower blood and tissue solubility coefficients than isoflurane (IF). Faster awakening from anesthesia has been observed in animal and initial clinical studies.[1,2] This study was conducted in the post-anesthesia care unit (PACU) to compare the recovery of cerebral cognitive functions from 0.65 MAC DF or IF anesthesia with 60% nitrous oxide in oxygen.

With institutional approval, 25 informed and consenting adult patients, ASA I, age 18-45, weighing 73 ± 10 (S.D.) kg, undergoing elective orthopedic surgery were studied. Preoperatively, the post-anesthesia recovery score (PARS), the Trieger Dot Test (TDT) and the Digit Substitution Test (DST) were explained to the patients, and baseline values obtained. Following midazolam 1-2 mg i.v. and oxygenation, patients were induced with thiopental 7 mg/kg and ventilated by mask to establish an adequate anesthetic level for intubation of the trachea without the use of muscle relaxant. The O_2, N_2O, end-tidal PCO_2, and inhaled and exhaled concentrations of DF or IF were monitored. During surgery, the end-tidal CO_2 was controlled between 32-35 mmHg; and the anesthetics at 0.65 MAC DF (4.6%, n=16) or IF (0.8%, n=9) with 60% N_2O. At the end of surgery, normal end-tidal CO_2 and neuromuscular function were restored and the anesthetics discontinued. The patient's cognitive functions were tested in the PACU every 15 minutes for 2 hours.

Patient's demographics and duration of anesthesia were similar between both groups. DF patients had significantly higher recovery scores for 45 minutes (Fig. 1). DF patients also demonstrated lower error responses of the TDT, as well as higher correct responses of the DST (Fig. 2).

In conclusion, cognitive functions recover from DF anesthesia significantly faster than from IF anesthesia. The differences may mean that patients will be "street-ready" earlier, a feature of particular value for outpatient surgery.

References:
1. Anesth Analg 66:977-82, 1987
2. Anesth Analg 70:S378, 1990

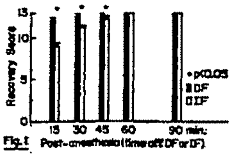


Fig.1

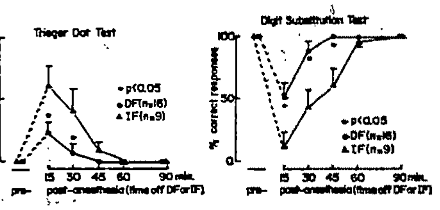


Fig. 2

S300

TITLE: ANALGESIC EFFICACY OF SACRAL EPIDURAL MORPHINE VS BUPRENORPHINE IN CHILDREN

AUTHORS: S.K. Tsai, M.D., M. Lippmann, M.D.,* K.T. Liao, M.D., M.S. Mok, M.D.*
AFFILIATION: Anes. Dept., *Harbor-UCLA Medical Center, Torrance, CA, 90509 and Department of Anesthesiology, National Yang-Ming Medical College, Taipei, Taiwan, R.O.C.

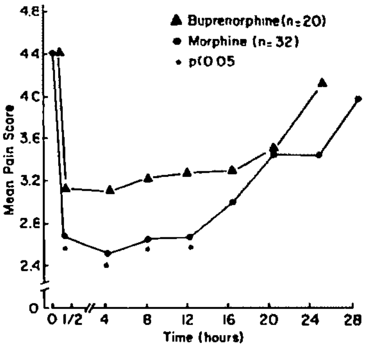
Epidural buprenorphine (B), has been shown to provide prolonged pain relief with less adverse side effects than morphine (MS) in adult patients (pts). The present study evaluated the efficacy and safety of B by sacral epidural injection vs MS for the relief of postoperative pain in pediatric pts.

After obtaining informed parental consent and with institutional approval, 52 pts ages 3-13 yrs, scheduled for elective abdominal surgery were enrolled. After induction with general ET anesthesia, an indwelling 10cm 23G epidural cath. was inserted (via a 5cm 19G Tuohy needle) through the sacral canal at the $S_{2\text{-}3}$ intervertebral space, threaded to the T_{12}-L_1 level and taped in place. In the postop period when the pts fully recovered from anesthesia and complained of severe pain, they were divided into 2 groups in a randomized double-blind fashion with Grp A (N=32) receiving epidural MS with a dose schedule of 1mg based on ideal body weight (IBW) for pts under 7 yrs, 1.5mg for those 7-10 yrs, and 2mg for those over 10 yrs. Grp B (N=20) pts received epidural B with a dose schedule of 45mcg (IBW) for pts under 7 yrs, 60 mcg for those 7-10 yrs, and 75mcg for those over 10 yrs. Pain relief was evaluated by the Krane, et al. (1) method. Vital signs, respiratory rate, and side effects were observed for 28 hrs.

Demographics and initial pain intensity were similar for both groups, as well as onset of pain relief (20 min). Epidural MS produced more potent analgesia (Fig.) with lower pain scores and a longer duration of action (18-24 hrs), vs 12-20 hrs for B. The mean dose of MS was 0.07mg/kg and that of B was 2mcg/kg IBW respectively. MS pts had a higher incidence of itching and urinary retention.

B provides efficacious pain relief but somewhat less than that of an equipotent dose of MS in the pediatric pt. Epidural B by the sacral route provided a very useful alternative for the control of postop pain in children.

REFERENCE:
1. Anesth Analg, 66:647-653, 1987.



S301

Title: HALOTHANE AND ISOFLURANE ATTENUATE LEUKOTRIENE-D_4 INDUCED CONSTRICTION OF THE GUINEA PIG TRACHEA

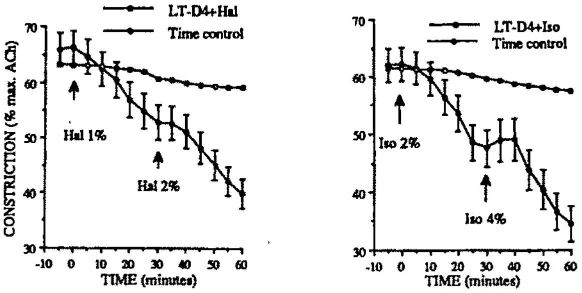
Authors: N. Tudoric M.D., R.L. Coon Ph.D., and Z.J. Bosnjak Ph.D.

Affiliation: Department of Anesthesiology, Medical College of Wisconsin and VA Medical Center, Milwaukee, WI.

Antigen induced constriction of the airway smooth muscle (ASM) is caused by mediators stored in pulmonary mast cells or by newly synthesized arachidonic acid metabolites, such as leukotrienes which are very potent constrictors.[1] Although the volatile anesthetics can prevent and reverse antigen-induced constriction of ASM,[3] the knowledge about the effects of volatile anesthetics on constriction induced by immune response mediators is, with exemption of histamine, limited. Therefore, we examined the effect of halothane (Hal) and isoflurane (Iso) on leukotriene-D_4 (LT-D_4) induced constriction of guinea pig tracheal smooth muscle.

After institutional approval, tracheal rings were excised from anesthetized guinea pigs, suspended and prestretched (3.0 g) in temperature controlled jacketed baths containing modified Krebs solution and bubbled with 95% O_2 and 5% CO_2 to maintain pH at 7.38-7.42 and PCO_2 at 35-40 mmHg. The constriction was induced with 1 nM of LT-D_4. After the constriction curve reached plateau, Hal or Iso were vaporized into a bubbling gas mixture. When equilibrated with 1 and 2% Hal for 30 min, the concentration in the bath was 0.26±0.01 and 0.5±0.02 mM, respectively. When bubbled with 2 and 4% Iso the concentration of Iso in the bath was 0.36±0.02 and 0.65±0.03 mM, respectively. To estimate possible indirect constrictive effects of LT-D_4, in some experiments tracheal rings were, prior the stimulation, incubated with atropine (1 µM), phentolamine (10 µM), and propranolol (5 µM). Three of eight tracheal rings from each animal were not exposed to anesthetics, and served as time controls. Constriction is expressed as percentage of maximal acetylcholine-induced constriction (mean±SE, n=14).

1% Hal reduced the constriction by 20.3, and 2% Hal induced additional relaxation of 24.5%. Iso 2 and 4% relaxed LT-D_4 induced constriction in similar manner by 23.5 and 27.5%, respectively (Figure). Since adrenergic and cholinergic blockers did not change the magnitude of constriction it is likely that LT-D_4 exerted its effect only via binding at specific receptor sites. Therefore, we conclude that Hal and Iso partially relaxed LT-D_4 induced constriction by direct effects on ASM, possibly by inducing membrane hyperpolarization.[3]



References: 1) Am Rev Resp Dis 136;985-999:1987.
2) Anesthesiology 156;107-111:1982.
3) Anesthesiology 60;309-318:1984.

S302

TITLE: EPIDURAL ANESTHESIA/ANALGESIA IMPROVES OUTCOME AFTER MAJOR VASCULAR SURGERY: A HYPOTHESIS RECONFIRMED

AUTHORS: KJ Tuman,M.D., RJ McCarthy,Pharm.D., R March,M.D., AD Ivankovich,M.D.

AFFILIATION: Depts.of Anesthesiology/Cardiovascular Surgery;Rush-Presbyterian-St. Luke's Medical Center;Chicago,IL

Choice of anesthesia for high-risk patients undergoing major vascular surgery remains controversial. Epidural anesthesia and analgesia (EAA) may be preferable to general anesthesia alone,(1) although some authors question whether choice of anesthesia is important in reducing morbidity.(2) This study further addresses the question of whether choice of anesthesia significantly affects outcome after major vascular surgery. After IRB approval, 80 consenting adults undergoing major vascular surgery of the abdominal aorta and lower extremities were randomly assigned to receive general combined with EAA using a continuous infusion of fentanyl and bupivacaine postoperatively (GEN-EPI), or "balanced" general anesthesia (isoflurane, N_2O, fentanyl) and parenteral narcotics for postop pain (GEN). Patient age, duration of surgery, EBL, incidence of preop angina, LV dysfunction, CHF, prior MI, arrhythmias, hypertension, renal insuff, COPD, DM, use of antianginal drugs, as well as the postop occurrence of cardiovascular (MI, CHF, ventricular or supraventricular tachyarrhythmias requiring treatment, angina, heart block), respiratory (prolonged intubation or reintubation), and major renal, GI, infectious, neurologic, and vascular graft complications requiring reoperation were noted. Data between groups was compared using χ^2 and Mann-Whitney tests. The anesthetic groups were demographically similar except that the GEN-EPI group tended to be older(69.6vs65.5yr,p=.05), with more DM (15/40 vs7/40,p=.04) & prior MI(19/40vs10/40,p=.04).

COMPLICATION	GEN (n=40)	GEN-EPI(n=40)	p VALUE
CV	11/40	4/40	.04
Respiratory	5/40	1/40	NS
Renal	3/40	1/40	NS
GI	1/40	2/40	NS
Infectious	8/40	2/40	.04
Neurologic	3/40	0/40	NS
Vascular graft failure	8/40	1/40	.03
*Total # complications	50	13	.01
Pts. w/ ≥1 complication	17/40	8/40	.03

*sum of individual components of CV + resp + others

The total # of complications and the # of patients experiencing ≥ 1 complication were significantly greater in the GEN group. There was no hospital mortality in either group. A multiple logistic regression model revealed that preop CHF and use of general anesthesia alone were the most significant predictors of serious cardiopulmonary complications in this study. These data reaffirm previous findings suggesting that EAA may significantly affect outcome in high-risk patients. EAA is associated with fewer serious complications than general anesthesia alone in this population. Differences from other studies (2) may be related to the continuation of EAA to provide postoperative analgesia.

References: 1) Yeager MP. Anesthesiology 1987;66:729.
2) Manolio T. J Clin Anesth 1989;1:414.

S303

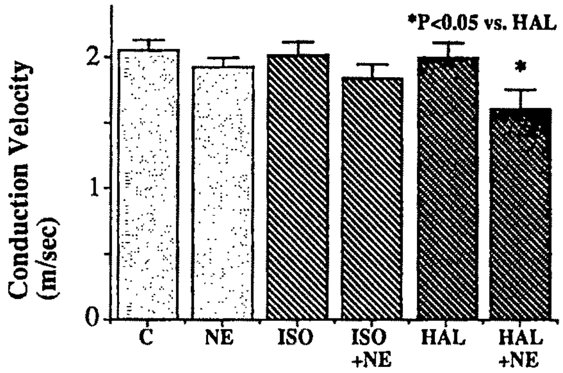
Title: DROMOTROPIC EFFECTS OF NOREPINEPHRINE ON CANINE PURKINJE FIBERS EXPOSED TO ISOFLURANE AND HALOTHANE

Authors: LA Turner, MD, A. Laszlo, MD, JP Kampine, MD, PhD, and ZJ Bosnjak, PhD.
Affiliation: Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI 53226

Arrhythmias often occur during anesthesia in association with increased sympathetic efferent nerve activity. It was reported that the negative dromotropic effect of halothane on Purkinje fibers is potentiated by epinephrine[1] which suggests that this adverse dromotropic effect may contribute to sensitization of the myocardium by halothane to the arrhythmogenic actions of catecholamines. The present study was designed to evaluate the effects of the neurotransmitter norepinephrine (NE) on conduction velocity (CV) of Purkinje fibers in the absence and presence of isoflurane (ISO) and halothane (HAL).

After institutional approval, free running false tendons were obtained from 16 canine hearts following sacrifice during halothane anesthesia. Segments 4-10 mm in length were mounted in a 2 ml chamber and superfused with Krebs solution equilibrated with 97% O_2-3% CO_2 (K^+4.0, Ca^{++}1.8 mM). Bipolar electrodes placed at one end of the tendons were used to stimulate the preparations at a CL of 400 msec. Two intracellular microelectrodes placed 4-8 mm apart were utilized to obtain Purkinje fiber action potentials. The upstrokes were amplified and displayed at fast sweep on a digital oscilloscope. CV was calculated from measured interelectrode conduction times and distance under each experimental condition. Krebs solution was preequilibrated with 2.0% ISO or 1.5% HAL, producing bath concentrations of 0.49 mM ISO and 0.44 mM HAL (gas chromatography). NE was added at a concentration of 10 μM. The actions of NE were compared in the absence (11 trials) and presence (12 trials each) of ISO and HAL utilizing ANOVA and Duncan's range test. A P level ≤ 0.05 was considered significant.

The actions of NE alone and in combination with ISO and HAL on conduction velocity (m/s ± SEM) are shown in the figure. NE alone and NE in the presence of ISO did not significantly reduce CV (changes of -6% and -9%, respectively). However, NE in the presence of HAL significantly decreased CV (-19%).



The findings indicate that NE tends to slow conduction in canine Purkinje fibers and that NE significantly slows conduction in the presence of HAL. The results suggest that the combination of NE with a "sensitizing" anesthetic like HAL has substantial negative dromotropic effects while the same adverse interaction may not occur with a "less sensitizing" agent like ISO.

Reference: 1) Res Comm Chem Path Pharmacol 40: 633,1974.

S304

TITLE: INTENTIONAL HEMODILUTION IN ANESTHETIZED PATIENTS REDUCES O2 DELIVERY

AUTHORS: P.Van der Linden MD, M.Wathieu MD, E.Gilbart MD, E.Engelman MD, JL Vincent MD, PhD
AFFILIATION: Anesth Dept, Erasme Hospital, Brussels, Belgium

During intentional hemodilution the decrease in arterial O2 content is usually compensated by an increase in cardiac output so that O2 delivery is maintained. This study was performed to better define the influence of anesthesia on these mechanisms using a modified pulmonary artery catheter allowing the determination of right ventricular (RV) volumes.

PATIENTS AND METHODS. After institutional approval, twenty patients scheduled for total hip replacement who gave their informed consent were included. All patients had normal preoperative LV and RV ejection fractions. After oral diazepam (0.1 mg/kg) catheters were inserted. Anesthesia was induced using fentanyl (3 μg/kg), thiopental (3 mg/kg), and vecuronium (0.1 mg/kg), and maintained with enflurane (0.5 to 1.0%). The patients were ventilated with an O2/N2O mixture (FiO2: 0.4). Patients were randomly assigned to hemodilution (H: N=10) or control (C: N=10). In the H group, isovolemic hemodilution was performed with HES 200/0.5 to achieve a hematocrit (Ht) of 30%. Measurements were obtained at baseline (T0), 15 min after induction (T1) and 10 min after hemodilution (H) or 40 min after T1 (C) (T2).

RESULTS. (Mean ± SD)

		T0	T1	T2
Hct (%)	H	39.4 ± 3.2	38.3 ± 3.1*	28.2 ± 1.4*
	C	39.8 ± 1.2	38.4 ± 1.6*	37.9 ± 1.0
HR (b/min)	H	75.5 ± 13.4	76.4 ± 11.8	62.5 ± 9.8*
	C	72.6 ± 9.4	69.2 ± 9.4	61.4 ± 9.0*
CI (l/min/kg)	H	3.3 ± 0.6	2.4 ± 0.4*	2.5 ± 0.5
	C	3.2 ± 0.5	2.3 ± 0.5*	2.2 ± 0.4
SI (ml/b/kg)	H	44.1 ± 8.1	33.1 ± 7.9*	39.3 ± 7.1*
	C	43.6 ± 3.7	33.5 ± 4.3*	35.6 ± 5.0
RVEF (%)	H	50.7 ± 7.5	44.2 ± 8.6	41.9 ± 7.1
	C	48.9 ± 8.8	42.3 ± 9.3*	40.7 ± 8.7
RVEDVI (ml/kg)	H	89.3 ± 23.9	73.8 ± 20.3	94.9 ± 18.5*
	C	91.6 ± 16.2	81.8 ± 16.1	89.7 ± 14.7
DO2 (ml/min/kg)	H	541.2 ± 88.9	388.5 ± 70.1*	311.0 ± 63.1*
	C	505.1 ± 73.1	361.6 ± 89.2*	347.9 ± 69.5

* = p<0.05 vs previous measurement.

DISCUSSION. In these conditions, normovolemic hemodilution under anesthesia resulted in an increase in RVEDVI but no change in CI, so that DO2 decreased. This was likely related to the effects of anesthetic agents on SI and HR.

S305

KETANSERIN IN THE TREATMENT OF POSTOPERATIVE HYPERTENSION:THE DUTCH MULTICENTER TRIAL

P.J.A. van der Starre, M.D., Ph.D.
Hospital De Weezenlanden, Department of Cardio-thoracic Anesthesia, Zwolle, The Netherlands

Introduction: Ketanserin, a selective S2-serotonergic receptor blocking agent with alpha1-receptor blocking properties (1), proved to be effective in the treatment of per and postoperative hypertension in patients undergoing coronary artery surgery (2). In a multicenter study, involving 30 anesthesia departments in The Netherlands, the effectiveness of ketanserin in the treatment of postoperative hypertension following general surgery was verified.

Methods: Informed consent and instutional approval were obtained for a prospective, double-blind, placebo-controlled trial in 280 patients (ASA 1 and 2) undergoing general surgery. All patients were awake.

Arterial blood pressure, heart rate (HR) and central venous pressure (CVP) were monitored. When systolic blood pressure (SBP) was higher than 150 mmHg in the early postoperative recovery period, ketanserin (K) or placebo (P) were administered as a bolus of 10 mg, followed by a continuous infusion of 4 mg/hour. When this treatment was not effective according to the opinion of the investigator, an alternative antihypertensive agent was administered, and the patient was excluded from further study.

Results: At the start of the study the K-group consisted of 143, and the P-group of 137 patients. At 10, 20 and 30 min both SBP and diastolic blood pressure (DBP) were significantly lower in the K-group. At 30 min 117 patients were left in the K-group, and 74 in the P-group. At 60, 90 and 120 min only SBP was significantly lower in the K-group. At 120 min 69 patients were left in the K-group, and 43 in the P-group. No significant differences in HR and CVP were found between the groups at any moment of recording.

Discussion: In this study ketanserin was found to be highly effective in the treatment of postoperative hypertension following general surgery. Ketanserin appeared to be a safe vasodilating compound, without causing hypotension or reflex tachycardia.

References
1. Lancet 5;297,1983
2. Anesth Analg 62;63,1983

S306

TITLE: COMPARATIVE EFFECTS OF ESMOLOL AND ALFENTANIL DURING PROPOFOL ANESTHESIA

AUTHORS: J. Van Hemelrijck, M.D., I. Smith, M.D., M. Poler, M.D., P. F. White, Ph.D., M.D.
AFFILIATION: Department of Anesthesiology, Washington University, St. Louis, MO 63110

Opioid analgesics are commonly used to block autonomic responses to endotracheal intubation and surgical stimulation. Unfortunately, opioids can also increase the incidence of postoperative nausea and vomiting, thereby delaying discharge after ambulatory surgery. This IRB-approved study was designed to compare the hemodynamic effects and recovery profiles when either alfentanil or esmolol was administered as an adjuvant during propofol anesthesia in the outpatient setting.

80 healthy, consenting outpatients undergoing plastic and orthopedic procedures were randomly assigned to receive either alfentanil (A) or esmolol (E) according to a double-blind protocol. A loading dose of E, 2 mg/kg, or A, 20 ug/kg, was administered over 2 min. using a Bard InfusOR pump followed by a variable-rate infusion titrated to maintain heart rate (HR), within 15% of baseline values. Anesthesia was induced with propofol, 2.5 mg/kg, and maintained with a propofol infusion, 0.05-0.2 mg/kg/min and 67% nitrous oxide. Data were analyzed using ANOVA and Chi-square tests, $p<0.05$ was considered significant.

The two groups were similar with respect to demographic data [age: 34±11(A) vs 35±12 yr (E), duration of surgery 61±20 vs 58±20 min]. Changes in HR and mean arterial pressure (MAP) were observed in both groups (table 1). However, A was associated with greater decreases in HR and MAP than E. The mean (± S.D.) propofol maintenance anesthetic requirement was also higher in the E group (0.14±0.02 vs 0.10±0.03 mg/kg/min). Although recovery times were similar (table 1), A-treated patients had higher sedation scores during the first hour after surgery. There were no significant differences between the two groups with respect to postoperative nausea, vomiting, or pain (table 2).

In conclusion, esmolol appears to be a viable alternative to alfentanil for use as an adjuvant during outpatient anesthesia.

Table 1: Intraoperative hemodynamic variables (means ± S.D.)

	HR (beats/min)		MAP (mm Hg)	
Event	A	E	A	E
Baseline	78 ± 12	82 ± 13	98 ± 13	100 ± 11
Postinduction	69 ± 10	71 ± 8	67 ± 10	79 ± 8**
Intubation	73 ± 11	81 ± 9*	87 ± 18	112 ± 17**
Preincision	63 ± 8	73 ± 8*	69 ± 8	78 ± 10*
Incision	62 ± 8	74 ± 9*	70 ± 9	76 ± 13*
Postincision	65 ± 8	71 ± 8	86 ± 12	86 ± 12

* $p < 0.05$; ** $p < 0.001$, E different from A.

Table 2: Recovery times and therapy for postop. side effects

	Awake (min)	Ambulate (min)	Discharge (min)	Antiemetics (%)	Analgesics (%)
A	10 ± 11	130 ± 56	147 ± 54	18	47
E	5 ± 8	124 ± 54	147 ± 63	7	62

S307

Title: EPIDURAL SUFENTANIL: EFFECT OF BUPIVACAINE ADDITION ON PAIN RELIEF CHARACTERISTICS IN RATS.

Authors: M. Vercauteren MD, T. Meert PhD, H. Adriaensen MD
Affiliation: Department of Neuropsychopharmacology, Janssen Research Foundation , B-2340 Beerse, Belgium.

Introduction: Adding opioids is a way to potentiate the analgesic activity of local anesthetics(1-2). In order to study the mechanisms of interaction between local anesthetics and lipophilic opioids, detailed dose-response functions were determined with bupivacaine and sufentanil alone or in different combination regimens.

Methods: The study was approved by the Institutional Committee for Animal Research. Male Wistar rats (n = 135) were equiped with an epidural catheter under general anesthesia. The rats were 4 days later randomly assigned to receive an epidural injection of 20 µl with either 40, 80, 160, 320 or 640 µg bupivacaine, 0.08, 0.16, 0.31, 0.63, 1.25 or 2.50 µg sufentanil, or the same doses of sufentanil combined with either 40 or 80 µg bupivacaine. Data were collected on 5 rats per drug treatment regimen. Tail withdrawal reaction time (TWR > 6.0 and ≥ 10.0 sec), blockade of pinna and cornea reflexes and muscle tone were scored repeatedly over time after injection. ED_{50}s were calculated according to Finney's iterative method. After the experiment, the catheter tip was checked at autopsy.

Results: The data are given in Table 1.

Discussion: The local anesthetic bupivacaine may potentiate the analgesic properties of the opioid sufentanil. Adding a by itself ineffective dose of 80 µg bupivacaine to sufentanil, results in a 2.2 to 3.0 fold decrease in ED_{50}s of sufentanil for analgesia. Furthermore, as compared to sufentanil alone, a 2.9 to 3.9 fold increase in the specificity ratio was obtained. However, no differences in duration of analgesia at comparable doses were measured. Lower doses of bupivacaine did not affect the activity of sufentanil. The combination of high doses of bupivacaine and sufentanil did not improve analgesia since adding 320 µg bupivacaine to 2.5 µg sufentanil did not result in a better analgesia or a prolonged activity, as compared to each drug alone. On the contrary, only the side-effects of both drugs were combined.

Therefore, these results indicate that local anesthetics at optimal concentrations may potentiate and improve the analgesic properties of lipophylic opioids such as sufentanil.

Table 1: Review ED_{50}s (µg) and other data.

Raw	Index	Suf	Suf + 40 µg Bupi	Suf + 80 µg Bupi	Bupi
A	TWR > 6.0 sec	0.19	0.19	0.085	171.6
B	TWR ≥ 10.0 sec	0.29	0.19	0.097	171.6
C	blockade Pinna	0.44	0.51	0.58	> 320
D	blockade Cornea	0.67	0.51	0.77	> 320
E	Rigidity	0.58	0.44	1.02	> 320
F	ratio C/A	2.32	2.68	6.82	
	C/B	1.52	2.68	5.98	
G	Duration (min) TWR ≥10.0 sec at 2 x ED_{50}	23.95	24.66	24.64	39.73

References:
1. Phillips, Anesthesiology 1987, 67, 835-838.
2. Cohen et al., Anesthesiology 1987, 67, 403-407.

S308

Title: ALFENTANIL DOES NOT POTENTIATE HYPNOTIC EFFECT OF PROPOFOL.

Authors: H R Vinik, MD, E L Bradley, Jr, PhD, I Kissin, MD, PhD
Affiliation: Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, Alabama 35294

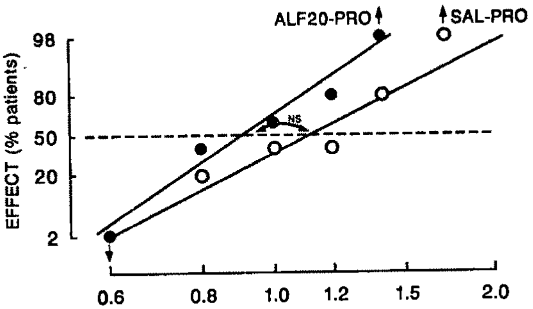
Alfentanil 0.02 mg/kg given to unpremedicated patients decreased the hypnotic ED_{50} value for midazolam from 0.270 mg/kg to 0.068 mg/kg(1). The aim of the present study was to determine whether induction of anesthesia with propofol could also be potentiated by the addition of alfentanil.

Fifty unpremedicated ASA physical status I or II adult female patients participated in the randomized, double-blind study, approved by the Institutional Human Investigation Committee. As an end-point of anesthesia the abolition of the ability to open eyes on command was used. Two groups of patients were used in the study: saline-propofol and alfentanil-propofol. The following predetermined doses of drugs each in a subgroup of five patients were administered. In the first group, the propofol doses were (mg/kg): 0.8, 1.0, 1.2, 1.4, 1.7. In the second group, alfentanil was used in a fixed dose of 0.02 mg/kg, and the propofol dose varied (mg/kg): 0.6, 0.8, 1.0, 1.2, 1.4. Dose-response curves were determined with the use of probit analysis.

The Figure represents propofol dose-response curves. The hypnotic ED_{50} value for propofol was 1.1 (95% confidence limits: 0.8, 1.4) mg/kg without and 0.9 (0.7, 1.1) mg/kg with the addition of alfentanil 0.02 mg/kg (NS for the difference).

It is a common anesthetic practice today to give small supplementary doses of opioids in conjunction with benzodiazepines or other hypnotic agents. Drugs such as alfentanil or fentanyl are given to enhance the analgesic component of anesthesia. With benzodiazepines they can also cause the profound enhancement of the hypnotic component of anesthesia. This potentiation does not occur when alfentanil is combined with propofol.

Reference: 1. Anesth Analg 1990;71:65, 1990.



Each dot represents the incidence of unconsciousness in a group of five patients.

S309

TITLE: ADENOSINE INHIBITS ACETYLCHOLINE RELEASE FROM THE MOUSE NEUROMUSCULAR JUNCTION THROUGH ADENOSINE RECEPTORS

AUTHORS: E.S. Vizi, M.D., Y. Ohta, M.D., F.F. Foldes, M.D.
AFFILIATION: Dept. of Anesthesiology, Montefiore Medical Center / Albert Einstein College of Medicine, Bronx, NY 10467 & Institute of Experimental Medicine, Budapest, H-1450, Hungary

Introduction. Adenosine inhibits neurotransmission at the neuromuscular junction (1,2), at parasympathetic and sympathetic transmission sites and in the central nervous system. In the present study, the role of presynaptic adenosine (A-1) receptors in the modulation of the evoked release of acetylcholine (ACh) at the neuromuscular junction was investigated by a radiochemical method (3).

Methods. The experiments were approved by the Institutional Animal Investigation Committee. Phrenic nerve-hemidiaphragm preparations of mice, mounted in 2 ml organ baths in Krebs' solution were loaded with ^{3}H-choline. Subsequently, the preparations were stimulated electrically (40 shocks at 50 Hz, every 10 sec for 3 min) twice, 30 min apart, and the amount of ^{3}H-ACh released during the two stimulation periods, S1 and S2, were determined.

Results. The data in the table (Mean±SEM of 6 experiments) indicate that adenosine and 2-chloroadenosine (CADO), added 18 min before S2, reduced the release of ^{3}H-ACh. 8-Phenyltheophylline (8-PT) by itself enhanced the release of ACh and prevented the inhibitory effect of CADO. Dipyridamole, an adenosine uptake blocker, inhibited the evoked release of ACh.

Discussion. Neurochemical evidence was obtained that the stimulation evoked ACh release from the mouse phrenic nerve-hemidiaphragm preparation is inhibited, via A-1 receptors, by adenosine and CADO. Their inhibitory effect was antagonized by the adenosine receptor antagonist, 8-PT. The observation that 8-PT alone increases and dipyridamole decreases the ACh release indicates that endogenous adenosine released by the nerve impulses also inhibits ACh release. Adenosine released from skeletal muscle during hypoxia may potentiate the effect of nondepolarizing muscle relaxants.

References.
1. Nature 232:63-64, 1971
2. J Physiol 346:243-256, 1984
3. Br J Anaesth 59:226-231, 1987

Compound (µM)	S2/S1	% Change
Control	0.78±0.04	-
Adenosine (100)	0.61±0.06*	-21.8
CADO (10)	0.40±0.04*	-48.7
8-PT (10)	1.18±0.09*	+51.3
8-PT (10) + CADO (10)	0.95±0.05*	+21.8
Dipyridamole (10)	0.57±0.05*	-26.9

*Significantly different from control (ANOVA followed by Duncan's test, p<0.05).

S310

Title: THE DIFFERENTIAL EFFECTS OF BUTORPHANOL, MEPERIDINE AND MORPHINE TREATMENT OF POSTANESTHESIA SHAKING

Authors: J. Vogelsang, R.N., Ed.D.*
S. R. Hayes, M.D., Ph.D.**
Affiliation: Dept. of Nursing, St. Elizabeth Medical Center* Dept. of Anesthesiology, University of Kentucky Medical Center**

Introduction: The cause of postanesthesia shaking (PS) is unknown. PS occurs during emergence in up to 67% of patients (1) at high physiological and psychological cost to patients. Several opioids are known to suppress PS (1-3). This study compared the effectiveness of butorphanol, meperidine and morphine in suppressing PS.

Methods: The Institutional Human Subjects Committee approved the two group study of 533 general anesthesia patients (18-89 yrs). PS developed in 120 patients (23%) within 60 mins of PACU arrival. PS was measured on a 0-3 scale (none to forceful) every 5 mins. Patients scoring 2 or 3 for 3-4 mins were divided into 4 treatment groups (n=66) and one nontreatment group (n=54) (Fig. 1). Nurses determined treatment following standard orders which consisted of IV butorphanol 1 mg (n=12), meperidine 15-30 mg (n=18, 23) or morphine 2-4 mg (n=13). Treatment effect was measured on a 0-2 scale (no change to disappeared) every min. Effective treatment was disappearance of PS within 5 mins without recurrence.

Results: By t-test, butorphanol was significantly more effective in suppressing PS within 2 mins than meperidine qiven for shaking, P<.02, or shaking and pain, P<.03 (Fig. 2). Morphine did not suppress PS.

Figure 1
GROUP DIVISION BY TREATMENT

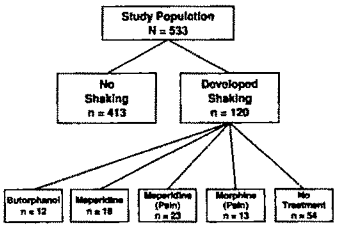
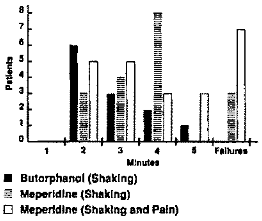


Figure 2
SHAKING SUPPRESSION BY ANALGESIC



Discussion: PS is an undesirable condition more effectively suppressed by butorphanol than meperidine. PS recurred in 3 patients and vomiting developed in 2 patients after receiving meperidine. Neither side effect occurred following butorphanol.

References:
1. Acta Anaesthesiol Scand 28:138-143, 1984
2. Anesth Analg 66:751-755, 1987
3. J Post Anesth Nur 4:222-227, 1989

S311

TITLE: ADVANTAGES IN POSTOPERATIVE RECOVERY OF LIGHT GENERAL/EPIDURAL ANESTHESIA

AUTHORS: P.N.H. Walmsley, MB, D. Kennedy, MD, H. Lynd, BS, B. Triplett, MD, F.J. McDonnell, MB, G. Colclough, MD, W.O. Witt, MD, N.W. Pedigo, PhD
AFFILIATION: Departments of Anesthesiology and Pharmacology, Univ. of Kentucky Medical Center, Lexington, KY 40536

After Institutional Review Board approval and consent, 79 patients scheduled for abdominal surgery were randomized to one of two types of general anesthesia. Group A (n=34) had a preoperative lumbar epidural placed at the L2-3 interspace with standard aseptic technique. General anesthesia was induced with sodium thiopental (4-5 mg/kg) and succinylcholine (1.5 mg/kg) for intubation, and maintained, with 50-70% nitrous oxide and 0.25-1.0% isoflurane. Other perioperative medications were iv fentanyl up to 100 µg, and midazolam up to 2 mg. Neuromuscular blockade was maintained using vecuronium and reversed with neostigmine 3 mg and glycopyrrolate 0.6 mg. Intraoperatively, a single dose of preservative-free morphine (2-3 mg) and intermittent lidocaine,(300 mg load, 150 mg/hour) were given epidurally, followed by bupivacaine (12.5 mg) just before closure. Group B (n=45) had a similar anesthetic, but received 1-2% isoflurane for maintenance and had no epidural. This group received iv morphine up to 6 mg titrated at the end of the case; they also received iv morphine for analgesia in post anesthesia care unit (PACU). Discharge was performed by PACU staff when the patients met standard criteria. The staff were unaware of the study.

Group A had significantly shorter PACU stays than did Group B (see table). Aldretescores on admission to PACU performed by recovery room nurses were not different (Group A = 8.4 ± 0.2; Group B = 7.8 ± 0.3). Visual analog scores (VAS) for pain at rest or after cough and sedation VAS were also significantly better in Group A (see table). Fewer patients in Group A were intubated on arrival in recovery room (13% vs 59%).

	Time in PACU (min)	VAS SCORES		
		Pain;Rest	Pain;Cough	Sedation
Group A	66 ± 4	5.4 ± 0.5	7.0 ± 0.5	6.1 ± 0.4
Group B	81 ± 4	7.3 ± 0.4	8.5 ± 0.3	7.4 ± 0.4
p value	<.02	<.01	<.01	<.03

Data are mean ± SEM assessed by one-way ANOVA.

This study demonstrates the advantages of a combined light general/epidural anesthetic over standard inhalational general anesthetic, in terms of reduced pain and sedation scores and shorter duration of PACU stay. The advantages of this technique for patient morbidity and hospital cost may support those previously reported by Yeager et al. (1).

References: 1. Anesthesiology 66:729, 1987

S312

Title: EPIDURAL EDTA INDUCES TETANIC CONTRACTIONS IN RATS

Authors: BC Wang MD[*], D Li MB[*], JM Hiller PhD[++], EJ Simon PhD[**], G Budzilovich MD[+], H Turndorf MD[*]
Affiliation: Depts of Anesthesiology[*], Pharmacology[**], Pathology[+] & Psychiatry[++] New York University Med Ctr, New York, NY 10016

Introduction: Disodium EDTA dihydrate, has replaced the antioxidant sodium bisulfite in 2-chloro-procaine Nesacaine CE, probably for preventing neurotoxicity. Enteral and parenteral EDTA administration has been associated with significant adverse effects including: teratogenicity(1), collagen fibril depletion(2), intestinal villi shortening(3), neural crest tumor formation and cell death in rats/mice(4), hepatic necrosis in calves(5) and contact allergy(6), vasculitis, cardiac tamponade, hemolytic anemia and renal damage in man.(7,8) The effects of Epidural (Epi) EDTA has not been examined. This study was undertaken to do this.

Method: With institutional approval, Epi catheters having an intraluminal volume of 0.02 ml were implanted through lumbar laminectomy in 3 groups of 6 500-600 gm male Sprague Dawley rats using 75-100 mg/kg intraperitoneal ketamine anesthesia. Animals received Epi injections (Inj) one week postsurgery. During daylight hours, on separate dates, each group of 6 rats was injected hourly with: G1 normal saline (NS) 0.1 ml pH=5. G2 0.0.1 ml of 0.05% Disodium EDTA pH=4.5, G3 0.1 ml of 0.1% Disodium EDTA. The total number of inj were G1:22-34, G2:25 and G3:15-26.

Results: G1 & G2 showed no sign of motor abnormality following NS or 0.05% EDTA Inj. One minute after 10th to 23rd Inj of 0.1% EDTA, 5 rats in G3 developed tetanic contractions of extremities, more on the lower, lasting 2-7 minutes. Tab 1. Histological examination of 2 rats after euthanasia revealed focal areas of nerve fiber degeneration of spinal roots.

Discussion: Data suggests that 0.1% Epi EDTA alters neurological function and is neurotoxic in rats. Compared with subarachnoid administration, tetanic contractions took more time to develop after Epi EDTA and only after 0.1% EDTA. In terms of dosage, 0.1 mg is 1/20 of the EDTA contained in a single Epi dose of Nesacaine in man. Accidental dura puncture is always a risk with epidural anesthesia. Drugs intended for Epi use could enter the subarachnoid space inadvertently. Therefore, incorporating EDTA in epidural anesthetics may be unwise before safety is established.

Table 1. Results of epidural 0.1% Disodium EDTA in rats (G3)

#	Inj	EDTA (mg)	TetaC	Recovery	Sacrifice
1	17	1.7	10th(4')	+	o
			12nd(2')	+	o
			15th(2')	+	o
2	22	2.2	14th(3')	+	o
			17th(2.5')	+	o
			19th(3')	+	o
3	26	2.6	16th(3')	+	o
4	18	1.8	12nd(5')	+	o
			15th(2')	+	o
			18th(6')		+
5	15	1.5	15th(7')		+
6	23	2.3		+	o

#=rabbit number, Inj=injection number, mg=EDTA mg, TetaC=tetanic contraction, (')=contraction duration

References:
1. Toxicol Appl Pharmacol 1986; 82:426-443
2. Pharmacol Res Commun 1988;20:133-146
3. Exp Mol Pathol 1978;28:215-226
4. Anat Anz 1988;166:209-217
5. J Am Vet Med Assoc1986; 188:406-409
6. Contact Dermatitis 1986;15:250-252
7. JAMA 1983;250:2926
8. JAMA 1983;250:672

S313

Title: **The Value of Thromboelastogram in Assessment of Postoperative Hemorrhage**

Authors: J-S Wang, M.D., W-T Hung, M.D., C. Y. Lin, M.D., B. Lee, M.D., R. Karp, M.D.
Affiliation: Departments of Anesthesia and Critical Care and Surgery, University of Chicago, Chicago, IL

Introduction: Despite the success of cardiac surgery, bleeding after cardiopulmonary bypass (CPB) is a serious problem that necessitates transfusion in a high percentage of patients and requires reexploration in about 3% of open heart patients. Many disorders such as thrombocytopenia, primary fibrinolysis defect in coagulation, and incorrect neutralization of heparin are frequently found in CPB patients, though only a small fraction of those patients will experience hemorrhage. The platelet count, prothrombin time (PT) activated partial thromboplastin time, and bleeding time are suggested as a standard screening hemostatic profile, although no one test is sufficient to make a specific diagnosis or to rule out all potential cause of bleeding. Recently thromboelastography (TEG) has been utilized to guide the therapy for correcting hemorrhagic problems.[1] Since our surgeons seldom request blood or component transfusion following coronary artery bypass surgery, we examined the usefulness of TEG in predicting the amount of chest drainage.

Method: Following Institutional Review Board approval, consecutive patients undergoing coronary artery surgery were studied. Before and after CPB, TEG was added to simple routine laboratory tests, including PT, aPTT, platelet count and hematocrit. We performed multifactorial analysis using chest tube drainage at four different periods (1, 6, 12, and 24 hrs) to determine the ability of laboratory (including TEG) variables in predicting postoperative bleeding.

Results: Multifactorial analysis revealed that there was no single factor or subfactor in TEG that correlated with the amount of chest tube drainage (Table).

Discussion: The management of patients with excessive hemorrhage following CPB can be difficult because of many variables, both surgical and nonsurgical. This study demonstrates that no laboratory data guide hemostatic care. Use of thromboelastogram in cardiac surgery neither provided timely information, nor information that enabled prediction of excessive hemorrhage after CPB.

Reference:

1. J Clin Monit 3:25, 1987

Table 1: Coefficients for correlation of chest tube drainage amount with TEG* and laboratory profiles after cardiac surgery

	1 hour	6 hours	12 hours	24 hours
ACT	0.136	0.068	0.050	0.065
Hct	0.083	0.197	0.219	0.260
PT	0.135	0.192	0.237	0.248
aPTT	0.245	0.185	0.211	0.248
Plt	0.145	0.319	0.370	0.398
R*	0.035	0.143	0.149	0.184
K*	0.176	0.201	0.227	0.213
MA*	0.124	0.139	0.170	0.185
Ma_{60}*	0.034	0.177	0.177	0.164

S314

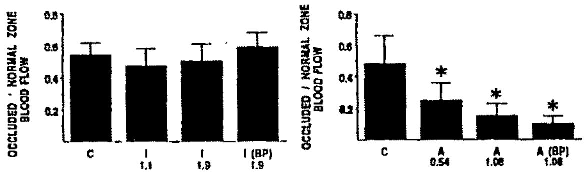
Title: MULTIVESSEL CORONARY ARTERY DISEASE WITH ENHANCED COLLATERALIZATION IN DOGS: ISOFLURANE vs. ADENOSINE

Authors: DC Warltler MD PhD, WT Schmeling MD PhD, JP Kampine MD PhD, JC Hartman BS
Affillation: Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee, WI 53226

Isoflurane (*I*) has been suggested to redistribute flow away from ischemic to normal myocardium independent of changes in systemic hemodynamics (coronary steal). This study compared the actions of *I* and adenosine (*A*) on myocardial perfusion in a chronically instrumented canine model of multivessel coronary disease with augmented collateral supply.

With prior approval of the Institutional Animal Care Committee, dogs were instrumented for measurement of myocardial blood flow (microspheres) and systemic hemodynamics. A hydraulic occluder and Ameroid constrictor were placed on the anterior descending (LAD) and left circumflex (LC) coronary arteries, respectively, to produce total LAD occlusion and chronic LC stenosis. After surgery, LAD and LC hyperemic responses to *A* were evaluated daily to monitor LC stenosis development. Simultaneous with stenosis advancement, the LAD was totally occluded for 2 min each hr for 8 hrs daily to stimulate collateral growth. When the LC flow response to *A* was reduced by at least 60% (postop day 11 ± 2) without change in LAD coronary reserve, the effects of *I* (N=8) or *A* (N=6) on hemodynamics and regional myocardial flow were evaluated. The LAD was totally occluded during LC stenosis and measurements made during the control (C) state and following *I* (1.1 and 1.9 %). In a separate group, similar measurements were made during infusions of *A* (0.54 and 1.08 mg/min) *via* a left ventricular catheter. Measurements were also made during the high concentration of either agent with arterial pressure adjusted to control levels (BP).

I significantly ($p<0.05$) reduced arterial pressure, left ventricular systolic pressure and +dP/dt_{50} without change in heart rate. *A* decreased arterial pressure and increased heart rate. Perfusion of occluded myocardium was approximately 50% of the normal zone (figure) and sufficient to sustain systolic shortening indicating an enhanced collateral circulation. *I* reduced flow to normal, stenotic and occluded zones but flow was maintained at conscious levels when arterial pressure was restored. *A* increased perfusion of normal and stenotic regions but decreased flow to the occluded zone which remained depressed during control of arterial pressure. Ratios of flow between occluded and normal regions remained unchanged by *I* but were reduced by *A* (figure).



The results indicate that *A* but not *I* produces coronary steal. When hypotension is corrected during *I*, myocardial perfusion is maintained at levels present in the conscious state.

S315

POSTOPERATIVE PULMONARY COMPLICATIONS: MORE COMMON WITH ENFLURANE THAN ISOFLURANE?

MA Warner, M.D.; ME Warner, M.D.; JG Weber, M.D.; KP Offord, M.S.; Departments of Anesthesiology and Biostatistics, Mayo Clinic, Rochester, MN 55905

Introduction: In a previous study on the effects of preoperative cessation of smoking, we noted an association between an increase in postoperative pulmonary complication (PPC) rate and the use of enflurane, but not isoflurane or halothane, in patients undergoing coronary artery surgery (CAS).[1] These agents were not, however, randomized in this earlier study because this association had not been previously reported. Therefore, we repeated our study and randomly assigned patients to receive either isoflurane or enflurane as anesthetic supplements to profound fentanyl analgesia to confirm or refute if choice of volatile anesthetic agent, in this setting, is associated with the development of PPCs.

Methods: With institutional approval, we prospectively studied 210 informed patients undergoing CAS. This study size was designed to have a statistical power of ≥ 0.9 in detecting a difference of approximately 20% in PPCs with an α-level of 0.05. Preoperative data included spirometry, blood gas analyses, and detailed smoking and cardiopulmonary assessments. PPCs, determined by a single blinded observer, have been previously described.[1] Univariate and multivariate analyses of these data for associations with PPCs used Chi-square and logistic regression techniques. Because of the previous association of enflurane and PPCs, one-tailed test values were used.

Results: After exclusion of 21 patients who failed the perioperative protocol for a variety of nonpulmonary reasons, 97 patients received isoflurane and 92 received enflurane. There were no statistical differences in these two groups. Overall PPCs developed in 29 and 34% of patients receiving isoflurane and enflurane, respectively (P=.151). Bronchospasm, however, developed more frequently in patients receiving enflurane, 17 vs 10% (P=.054). The 95% confidence interval for this difference was -18.2 to 1.8%. In both groups, the presence of PPCs prolonged hospitalization (P=.034).

Discussion: This study confirms the trend noted in our earlier study[1] that patients receiving enflurane compared to isoflurane in this setting appear to have a greater risk of developing bronchospasm. Enflurane has been reported to produce greater pulmonary histopathologic changes in a viral influenza-infected model than several other volatile anesthetics.[2] These changes of epithelial necrosis and sloughing, if present in humans, may contribute to bronchial plugging, airway irritation, and the development of bronchospasm, but this etiology is not confirmed by our study.

References: 1. Mayo Clin Proc 64:609-616, 1989
2. Anesth Analg 67:671-676, 1988

S316

TITLE: EFFECT OF PROPOFOL ON POSTOPERATIVE VOMITING AFTER STRABISMUS SURGERY

AUTHORS M.F. Watcha, M.D.,*P.F. White, Ph.D., M.D.,* F.C. Chu, M.D.**J.L. Stevens, M.D.**,
AFFILIATION: Departments of Anesthesiology* and Ophthalmology**, Washington University, St. Louis, MO 63110

Postoperative vomiting occurs in 40-80% of pediatric patients undergoing strabismus surgery (1). Propofol, a new IV anesthetic, is associated with a rapid recovery and a low incidence of postoperative vomiting (2). Some investigators have suggested that propofol may possess specific antiemetic properties. This study was designed to determine if the use of propofol (vs halothane) for maintenance of anesthesia would decrease the incidence of vomiting after pediatric strabismus surgery.

After obtaining IRB approval and parental consent, we studied 76 ASA I-II pediatric outpatients undergoing strabismus surgery. Following a standardized induction with halothane and nitrous oxide (N_2O) in O_2, patients were randomly assigned to one of 4 treatment groups: Group A (control)-halothane 1-2% + N_2O 66% + droperidol 75 µg/kg; Group B-propofol, 2 mg/kg followed by 5-10 mg/kg/hr; Group C- propofol (as in group B) + N_2O 66%; Group D-propofol (as in group B) + N_2O 66% + droperidol 75 µg/kg. Halothane and propofol dosages were adjusted to prevent signs of inadequate anesthesia. At the end of the operation neuromuscular blockade was reversed, the stomach was evacuated and the trachea extubated. Severe postoperative vomiting (at least 2 episodes in 1 hr or 3 episodes in 3 hr) was treated with metoclopramide 0.2 mg/kg IV, and if necessary with rectal trimethobenzamide.

The four groups were comparable with respect to age, weight, number of eye muscles repaired, and duration of surgery and anesthesia. The table includes data on the incidence of emesis during a 24 hr postoperative period. All times are means (± SD) from the end of surgery.

Group	A	B	C	D
N	20	18	18	20
Extub. time (min)	13.9 ± 8.6	11.3 ± 7.3	11.2 ± 5.2	10.4 ± 5.4
Eye opening (min)	41.6 ± 24.0	28.9 ± 18.8*	26.7 ± 14.9*	30.3 ± 17.6
Oral intake (min)	223 ± 105	134 ± 57*	141 ± 54*	221 ± 111
Dischg time (min)	341 ± 99	271 ± 84*	340 ± 129	347 ± 81
Emesis (%)	40%	22%	66%□	50%
Severe emesis (%)	5%	11%	22%	10%
Emesis in hosp (%)	20%	17%	55%*□	40%
Emesis at home (%)	20%	11%	33%	35%

* $p < 0.05$ vs Group A □ $p < 0.05$ vs Group B.

Children undergoing strabismus surgery with propofol anesthesia have decreased times to awakening, oral intake and discharge compared to a control group receiving a standard inhalation anesthetic with prophylactic droperidol. However, these data suggest propofol treated patients have the same incidence of postoperative emesis as the control group. While N_2O appears to increase emetic sequelae when used in combination with propofol, droperidol decreases vomiting after propofol-N_2O anesthesia.

In summary, when used for maintenance of anesthesia, a propofol-N_2O-droperidol combination is as effective as halothane - N_2O - droperidol in decreasing the incidence of vomiting following strabismus surgery. The use of a total IV anesthetic technique (Group B) may further decrease the incidence of postoperative vomiting in this surgical population.

References 1. Patel RI et al. Anesthesiology 69:1009, 1988 2. Gunawardene RD et al. Anaesthesia 43:65, 1988

S317

Title: A RE-EVALUATION OF THE PENTOTHAL TEST TO DETECT CSF IN THE EPIDURAL CATHETER ASPIRATE

Authors: JJ Waters M.D., S Ramanathan M.D.
Affiliation: Dept of Anesthesiology, New York University Medical Center, New York, NY 10016

Introduction: The ability of local anesthetics to form a precipitate (ppt) with pentothal is used to distinguish them from CSF. The use of epidural narcotics has become popular. This study reassess the pentothal test in vitro in the presence of local anesthetics, narcotics, and normal saline (NS, drug diluent) and CSF.
Methods: The protocol was reviewed by the institutional review board and patients consented to withdrawal of CSF. The pH of the following solutions was determined: Preservative free morphine sulfate 1 mg/ml (MS-1), morphine sulfate 0.5 mg/ml (MS-0.5), fentanyl 100 μg/ml (Fent), preservative free NS, bupivacaine 0.5% (Bupi), lidocaine 2% with freshly added 1:200,000 epinephrine (Lido) and CSF pooled from 4 pregnant patients. The local anesthetics were diluted with CSF, narcotics or NS 1:1, 1:2, 1:5 or 1:10 (final volume 1 ml) and tested with pentothal 2.5% 100 μl. In addition, the pH of the mixture was measured before and after addition of pentothal. Pentothal test was also done on undiluted local anesthetic, narcotic, NS and CSF.
Results: The pH of pentothal was 9.55 and the pH of CSF was 7.4. MS-1, MS-0.5 and Fent, NS had an acidic pH (Table 1) and yet they did not form a ppt with pentothal. Both local anesthetics formed a ppt with pentothal alone or when mixed with MS-1, MS-0.5, Fent in 1:1, 1:2 and 1:5 dilutions but not at 1:10 dilution (Table 2). All dilutions of both local anesthetics in CSF precipitated with pentothal.
Discussion: Data show pH of the solution alone is not a critical factor in pentothal precipitation. Stronger H^+ donors (local anesthetics) precipitate with pentothal more readily than do weaker ones (narcotics, NS) despite similar pH. Pentothal, a strong alkali, raises the pH of weak H^+ donors, leading to higher postpentothal pH and no ppt. Even a small amount of local anesthetic present in CSF could cause a ppt with pentothal (false negative for CSF). Similarly narcotic or NS could be mistaken for CSF (false positive for CSF). Local anesthetic diluted with MS, Fent or NS could be mistaken for CSF. False negative results are more dangerous than false positive results. Thus the pentothal test for distinguishing local anesthetics from CSF is of questionable value.

Table 1: pH and precipitation characteristics with pentothal

Drug	pH	Ppt with pentothal
Bupivacaine 0.5%	4.9	Yes
Lidocaine 2% (epi)	6.1	Yes
Morphine 1 mg/ml	5.7	No
Morphine 0.5 mg/ml	6.05	No
Fentanyl 100 μg/ml	6.3	No
CSF	7.4	No
Diluent normal saline	5.4	No

Table 2: Lidocaine/bupivacaine precipitation with pentothal

	1:1 dilution			1:10 dilution		
Diluent	pH-1	Ppt	pH-2	pH - 1	Ppt	pH-2
MS-1	6.1	Yes	7.58	6.4	No	8.25
CSF	7.0	Yes	7.5	7.38	Yes	8.45

Legend: pH-1 - before pentothal; pH-2 - after pentothal.

S318

Title: THE EFFECTS OF ANESTHETICS ON PROTEINASE INHIBITORS IN C57BL/6 MOUSE

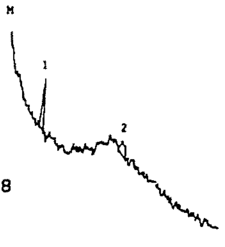
Authors: B. Waxler, MD, X. Zhang, MS, F. Wezeman, PhD
Affiliation: Hektoen Institute Of Cook County Hospital & Loyola University, Chicago, Il.

Work funded by I.A.R.S.

A family of proteinase inhibitors in many tissues including lung are part of a vital homeostatic mechanism to control invasive processes like tumors. Our purpose was to develop an animal model to study new clinical implications including the use of anesthetic agents which enhance proteinase inhibitory activity in cancer patients or smokers with depressed levels of low molecular weight proteinase inhibitors (1, 2).
Methods: Approval was obtained from the institutional Animal Investigation Committee and their requirements were met. Male (Ma) or female (F) mice C57BL/6 (8-10 weeks old) were randomly assigned to six groups: (1) Ma anesthesized with Ketamine (K) (2) F anesthesized with K (3) Ma anesthesized with Halothane (H) (4) F anesthesized with H (5) Ma not exposed to H or K (6) F not exposed to H or K. Ultrafiltration of extracts of lungs of each group yielded a final concentrate (FC) (molecular weight, MW, between 1,000 and 50,000). Quantification of both the inhibitory activity by TAME (p-tosyl-L-arginine methyl ester) method and protein were performed on each FC. TAME was analysed statistically with the t-test to compare percent inhibitory activity per ug of protein. After affinity chromatography of FC with immobilized trypsin, high performance liquid chromatography (HPLC) was performed on each eluate. The peaks were compared to known MW standards including myoglobin (M) and bovine pancreatic trypsin inhibitor (BPTI, MW 6,500).
Results: FC from F mice exposed to H had more proteinase inhibitory activity (p less than 0.05) than those from unexposed F mice. FC from F mice exposed to H had greater inhibitory activity (p less than 0.05) compared to those from Ma mice exposed to H. No significant difference is detected between the remaining groups. Analysis of HPLC indicated that the eluate had a major peak 1 with a MW comparable to that of BPTI.
Discussion: A previous study suggests that normal tissues may possess significantly more proteinase inhibitory activity than malignant tissues (1). Anesthetics may affect the proteinase-proteinase inhibitor balance between invasive processes, including local ingrowth of metastatic tumors in lungs, and adjacent normal tissue. The use of anesthetic agents (like H) which increase proteinase inhibitory activity may be preferred for cancer patients, especially females.

Table: TAME Data (Means)

Group 1	Ma	K	0.235
Group 2	F	K	0.192
Group 3	Ma	H	0.136
Group 4	F	H	0.512
Group 5	Ma		0.227
Group 6	F		0.121



References:
1. J Lab Clin Med, 1984;104:528
2. Eur J Respir Dis, 1985: 139(S): 62

S319

ALFENTANIL-INDUCED MUSCLE RIGIDITY IS ANTAGONIZED BY CENTRAL ADMINISTRATION OF KAPPA AGONISTS IN THE RAT

M. B. Weinger, M. D., V. Motis, B. S., S. Negus, Ph. D.
Dept. of Anesthesiology, UCSD and VAMC, San Diego, 92161

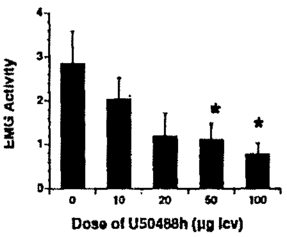
Opiate-induced muscle rigidity has become a significant clinical problem since the introduction of more potent and selective mu agonists such as alfentanil (ALF). Ongoing studies in our laboratory suggest that rigidity may primarily be mediated by mu-2 opioid receptors [1]. Previous work has suggested that kappa agonists can act as mu-2 antagonists [2]. In this study we examined the effect of central administration of a selective kappa agonist [U50488h] on ALF-induced rigidity in spontaneously ventilating rats.

Methods After Animal Care Committee approval, 52 anesthetized male Wistar rats had 7-mm, 23-gauge steel guide cannulae implanted stereotaxically 1 mm above the lateral ventricle [3]. Following three 1-hour conditioning sessions and a 5-day recovery, an 8-mm injector was inserted into the guide cannula and a 10 µl "blinded" intraventricular (ICV) injection of either saline or U50488h (10-100µg) was made. Following opiate or saline administration in each experiment, muscle rigidity was measured by electromyographic (EMG) activity from the left gastrocnemius muscle [4]. After a 15 min baseline, the rats were injected with ALF (0.5mg/kg s.c.) or saline, and data were then collected every 5 min for 60 min. For each group, the mean (±SEM) of the area under the normalized EMG voltage-versus-time curve was calculated. Statistical differences ($P<0.05$) were assessed using one-way ANOVA followed by Newman-Keuls *a posteriori* tests.

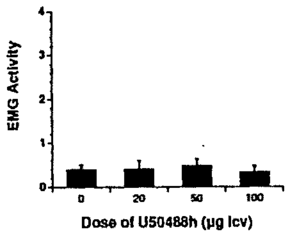
Results The addition of ICV U50488h dose-dependently decreased the magnitude of ALF rigidity, attaining significance at 50 µg (* on **Figure**). In contrast, U50488h in the absence of ALF failed to affect EMG activity. U50488h did not antagonize ALF's anesthetic effects.

Discussion ICV administration of the kappa agonist, U50488h, antagonized ALF rigidity yet, on its own, had no effect on muscle tone. Since U50488h was administered directly into the brain, these effects are centrally-mediated. Augmentation by U50488h of ALF's cardiorespiratory depression as the cause of decreased muscle tone seems unlikely since a previous, similarly designed, study using the potent mu agonist DAGO demonstrated an increase rather than a decrease in ALF rigidity [5]. These data are consistent with the hypothesis that mu-2 opioid receptors play the major role in mediating opiate-induced rigidity [1]. Thus muscle rigidity may be pharmacologically separable from mu-1 opiate effects such as analgesia and reinforcement on the basis of opioid receptor subtype specificity.

Effects of U504€8h on ALF Rigidity



Effects of U50488h Alone



References
1. Weinger MB, et al: Anesthesiology 1990 (in press).
2. Porreca F, Tortella FC: Life Sci 41: 2511, 1987.
3. Vaccarino FJ, et al: Pharmacol Biochem Behav 23: 495, 1985.
4. Weinger MB, et al: Pharmacol Biochem Behav 29: 573, 1988.
5. Bronson JB, et al: Anesthesiology 71: A600, 1989.

S320

Title: COMPARISON OF DESFLURANE AND HALOTHANE ANESTHESIA IN PEDIATRIC AMBULATORY PATIENTS

Authors: L Welborn, MD, M Zwass, MD, C Coté, MD, P Davis, MD, M Dinner, MD, R Hannallah, MD, W McGill, MD, D Fisher, MD, L Liu, MD, R Cook, MD, J Sarner, MD
Institutions: CNMC, Wash., DC; UCSF, CA; MGH, MA; CHP, PA and Cornell U, NY

Introduction: This open randomized study compares the induction, maintenance, and recovery characteristics of desflurane (I-653) vs. halothane in children.

Methods: With institutional approval and parental consent, 43 healthy children age 1 mo to 12 yr were studied. Patients were randomized to receive desflurane (D) or halothane (H) for induction and/or maint. of anesthesia in one of 4 possible combinations: D/D with and without oral premedication, H/H, or H/D. N_2O/O_2 was used as the carrier gas in all cases. Quality and speed of induction, time to awakening, recovery and discharge were compared in all groups.

Results: Induction and recovery times are shown in the table. Breathholding, coughing, secretions were significantly more frequent during desflurane inductions. Premedication did not modify that response. Cardiovascular and metabolic effects of the two anesthetics were similar in all groups.

Table: Patients' Age, Induction and Recovery times in the Study Patients

Variable (mean ± SD)	D/D (n=17)	H/D (n=12)	H/H (n=14)	ANOVA P
Age (mo)	45 ± 40	39 ± 42	37 ± 33	> .8
Minutes to Loss of eyelash reflex	1.7 ± .5	1.7 ± .4	2.0 ± .4	> .2
Min. to Intubation	6.1 ± 2	5.6 ± 1	6.9 ± 3	> .2
Min. from D/C of anesthetic to:				
Awake in OR	3.7 ± 1.7	3.7 ± 1.6	8.6 ± 3.8	< .001
Recovery in PACU	11 ± 8	11 ± 9	29 ± 12	< .00001
Discharge Home	184 ± 40	168 ± 36	171 ± 35	> .4

Discussion: The low blood-solubility of desflurane resulted in rapid emergence from anesthesia even following halothane induction. However, the tendency for desflurane to induce coughing and laryngospasm limited the rate at which it could be administered during induction of anesthesia and resulted in an unacceptably high incidence of serious airway complications. More studies are needed to establish the usefulness of this new agent in Pediatric Anesthesia.

S321

TITLE: ORAL MIDAZOLAM-MEPERIDINE-ATROPINE PREMEDICATION IN PEDIATRIC OUTPATIENTS

AUTHORS: B.C. Weldon, M.D., P.F. White, Ph.D., M.D.
AFFILIATION: Department of Anesthesiology, Washington University, St. Louis, MO 63110

Oral midazolam (MDZ) has been shown to be a safe and effective premedicant for children. Although meperidine (MEP) is commonly used in combination with benzodiazepines, its effects when combined with oral MDZ are unknown. In this placebo-controlled, double-blind IRB-approved study, we examined the effects of MEP and MDZ when administered alone and in combination as oral premedicants prior to ambulatory surgery.

141 parental-consented ASA I-II children, aged 1-8 years, undergoing a variety of outpatient procedures were randomly assigned to one of four treatment groups: Group I (control) received apple juice 0.2 ml/kg; Group 2, MEP 1.5 mg/kg in juice, Group 3, MDZ 0.5 mg/kg in juice; and Group 4, MEP 1.5 mg/kg with MDZ 0.5 mg/kg in juice. All patients received atropine, 0.02 mg/kg po. Cardiorespiratory variables (HR, RR, SaO_2) and sedation level were determined at the time of premedication and at 15 min intervals until the child entered the operating room. Separation [satisfactory = separates easily, non-clinging; unsatisfactory = crying, clinging, combative] and induction [satisfactory = unafraid, accepts mask; unsatisfactory = fear of mask, crying, combative] scores were used to evaluate the child's reaction to separation from their parents and to a mask induction with halothane/N_2O. Data were analyzed using ANOVA and Chi-square tests, with p<0.05 considered significant.

The four treatment groups were similar with regard to demographic data. Neither MEP, MDZ, nor the MEP-MDZ combination produced any significant changes in RR or SaO_2. No differences in sedation, separation or induction scores were found between those patients given MDZ alone and those who received a combination of MEP and MDZ. Both MDZ and MEP-MDZ were superior to MEP alone and to the placebo in facilitating separation and induction (table). The incidence of postoperative agitation and vomiting was similar in all four treatment groups. However, the length of the PACU stay was significantly longer for children who received the MEP-MDZ combination compared to the other groups.

In conclusion, the use of a combination of meperidine, midazolam, and atropine is safe and effective. However, it has no apparent advantage over midazolam and atropine alone for premedication in the outpatient setting.

	CONTROL	MEP	MDZ	MEP-MDZ
Separation				
Satisfactory	75%	75%	95%*	92%*
Unsatisfactory	25%	25%	5%	8%
Induction				
Satisfactory	56%	67%	88%*	92%*
Unsatisfactory	44%	33%	12%	8%
Recovery				
Awakening (min)+	9±10	9±7	15±12	12±16
PACU stay (min)+	29±11	29±12	28±20	39±19**
Postop agitation(%)	40%	40%	38%	33%
Vomiting (%)	28%	29%	19%	28%

* Significant difference from Gp 1 and 2; **Gp. 1, 2, and 3, p<0.05
+ Mean values ± S.D.

S322

TITLE: FLUMAZENIL REVERSES MIDAZOLAM-INDUCED VENTILATORY DEPRESSION IN MAN

AUTHORS: R.S. Weller, M.D., P. Conard, CRNA, J.B. Gross, M.D.
AFFILIATION: Department of Anesthesiology, University of Connecticut School of Medicine, Farmington, CT 06030

Introduction: Flumazenil (FLU), an experimental benzodiazepine antagonist, effectively reverses midazolam (MDZ) induced sedation[1]. We performed the present study to determine if it also reverses MDZ-induced ventilatory depression.

Methods: Twelve healthy male volunteers consented to participate in this IRB-approved study. On each of 2 study days, we performed pre-MDZ ventilatory measurements (v.i.), then administered MDZ, 0.01 $mg \bullet kg^{-1} \bullet min^{-1}$ i.v. until patients failed to respond to verbal command. After obtaining post-MDZ ventilatory measurements, we administered a study drug (1.0 mg of FLU or an equal volume of FLU vehicle) i.v. in a randomized, double-blind fashion. We repeated the ventilatory response measurements 3, 30, 60, and 120 minutes after study drug. Seven to 30 days later, we repeated the study sequence, with subjects receiving placebo or FLU, whichever they had not received previously. For each ventilatory measurement, we determined the slope of the CO_2 response curve using Read's rebreathing technique. After each rebreathing test, we performed a steady-state test by holding $P_{ET}CO_2$=46 mmHg for 6 min before measuring minute ventilation ($\dot{V}_E46$)[2]. We compared the effect of FLU and placebo on ventilatory variables with 3-way ANOVA and the protected least significant difference test. Values are shown as x±SEM; P<0.05 indicated significance.

Results: Midazolam significantly decreased both slope and $\dot{V}_E46$ (figures 1,2; P<0.01). Three minutes after administration, neither FLU nor placebo significantly affected the slope of the CO_2 response. $\dot{V}_E46$ did not increase significantly after placebo, but returned to its pre-MDZ value within 3 min of FLU administration (P<0.005 between groups, figure 2); the between-group difference in $\dot{V}_E46$ remained significant 30 min after study drug (P<0.05). Sixty min after study drug, neither slope nor $\dot{V}_E46$ differed significantly between FLU and placebo.

Discussion: MDZ decreased both the slope of the CO_2 response and $\dot{V}_E46$ by about 1/3.[2] The primary effect of FLU was to return $\dot{V}_E46$ to its pre-MDZ value without a significant change in the slope of the CO_2 response. Therefore, in MDZ-sedated patients, $\dot{V}_E$ at clinically relevant CO_2 tensions will be greater after FLU than after placebo. The fact that FLU primarily affects the displacement rather than the slope of the CO_2 response explains why previous investigators, who used Read's rebreathing technique alone, could not demonstrate ventilatory improvement following FLU.[1] Flumazenil's ability to antagonize MDZ-induced ventilatory depression may acutely reduce the risk of hypoventilation; however, fig. 2 suggests that this effect may diminish within 60 min.

References: [1] Anesthesiology 67:A534, 1987.
[2] Anesthesiology 58:540-4, 1983.

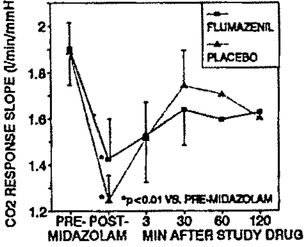


Figure 1

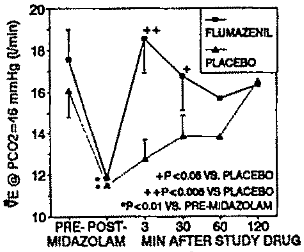


Figure 2

S323

Title: SPEED OF ANALGESIC ONSET: PLACEBO-CONTROLLED STUDY OF KETOROLAC AND TWO DOSES OF MORPHINE

Authors: E Whitehead FFARCS, G O'Sullivan FFARCS, CG Miller PhD, RES Bullingham FFARCS
Affiliation: St. Thomas' Hospital, Lambeth Palace Road, London SE1, UK.

INTRODUCTION: Standard post-operative pain models estimate the time of onset of analgesia from assessments performed at defined times. These may be too imprecise to determine the true time of onset of analgesia. We have developed a model which records changes in pain intensity at frequent intervals.

METHODS: Institutional Review Board approval was obtained and all patients gave informed consent.

105 alert patients suffering moderate pain and requiring parenteral analgesia within 2 hours of anaesthesia randomly received a 1.5 ml intravenous injection of ketorolac tromethamine 10mg, morphine 10mg, morphine 5mg, or placebo (the ketorolac vehicle). They were evaluated pre-drug injection and for 1 hour afterwards during which 14 verbal pain intensity measurements were recorded. If pain relief appeared insufficient, "rescue" analgesia was given.

The time of onset of analgesia was expressed as the time at which 25 or 50% of patients obtained 25 or 50% pain relief. Statistical comparisons were made using appropriate non-parametric methods.

RESULTS: The mean pain severity scores prior to drug injection were similar for the 4 groups.

The onset time of analgesia (minutes) for the 4 groups is shown in the Table. In general, the speed of onset was morphine 10mg, morphine 5mg, ketorolac and placebo. Ketorolac was not significantly different from placebo.

Table. Time (minutes) to onset of 25% and 50% pain relief for 25% and 50% of patients

	25% pain relief		50% pain relief	
% of patients	25%	50%	25%	50%
Morphine 10mg	1.8	4.0	6.0	13.9
Morphine 5mg	4.0	9.1	15.0	>60.0
Ketorolac	9.7	33.2	20.0	>60.0
Placebo	6.0	>60.0	40.0	>60.0

S324

TITLE: HYPERCARBIA DEPRESSES EEG MAGNITUDE DURING CARDIOPULMONARY BYPASS IN MAN

AUTHORS: WK Williamson BSc, RC Roy MD PhD, AT Rogers MD, DS Prough MD, D Charles CCP
AFFILIATION: Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, NC 27103

INTRODUCTION: During hypothermic cardiopulmonary bypass (CPB), hypercarbia decreases cerebral oxygen consumption ($CMRO_2$) (1). We hypothesized that a lower $CMRO_2$ would be associated with less electroencephalographic (EEG) activity than a higher $CMRO_2$. We report EEG changes associated with two different levels of $PaCO_2$ (40 mmHg uncorrected vs 40 mmHg corrected for temperature [57 mmHg uncorrected for temperature]) during otherwise stable CPB.

METHODS: After IRB approval and informed consent from 24 cardiac surgical patients, we monitored 4-channel computer-processed EEG (Tracor Nomad) using gold cup electrodes in a bilateral frontal-central-temporal montage according to the international 10-20 system. Impedances were below 2000Ω. Anesthesia was induced with fentanyl (50 μg/kg) and midazolam (.05 mg/kg) and maintained with constant infusions of both agents. Spectral edge frequency (SEF, Hz) and magnitude (μV^2) were recorded at two 1-min intervals during stable hypothermic CPB: first, 5 min after reaching 28°C and second, 20 min later. Subjects were equally and randomly divided into 4 groups according to $PaCO_2$ management during hypothermic CPB: Group I $PaCO_2$ was maintained initially at 40 mmHg, then increased to 57 mmHg; group II $PaCO_2$ was maintained first at 57 mmHg then decreased to 40 mmHg; group III remained at 40 mmHg for both measurement intervals; and group IV $PaCO_2$ remained at 57 mmHg for both intervals. All gas tensions are uncorrected for temperature. Results were analyzed using paired t-tests ($p<.05$ significant).

RESULTS: In all groups, temperature, blood pressure, and pump flow were constant. SEF tended to decrease in all 4 groups. Magnitude was unaltered in groups III and IV, consistent with the reported stability of $CMRO_2$ during hypothermic CPB (2). Magnitude fell significantly in group I as $PaCO_2$ increased from 40 to 57 mmHg. Within group II, magnitude increased as $PaCO_2$ fell from 57 to 40 mmHg but did not achieve statistical significance ($p=.067$) (Figure).

DISCUSSION: The observed EEG changes support our directional hypothesis that hypercarbia during hypothermic CPB, a condition associated with decreased $CMRO_2$, is associated with EEG suppression. Decreased $CMRO_2$ may confer some cerebral protective effect (3). More data are needed to determine whether electrophysiologic evidence of cerebral depression is also evidence of improved neurologic outcome.

REFERENCES: 1. Rogers et al. Anesth Analg 1988;67:S187; 2. Rogers et al. Anesth Analg 1989;68:S236; 3. Woodcock et al. Anesthesiology 1987;67;218

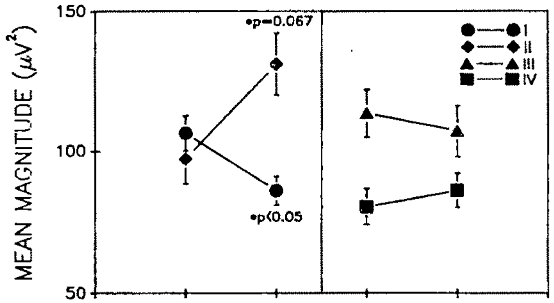


FIGURE: Mean magnitude ± SEM, time 1 versus time 2

S325

Title: HISTAMINE RELEASE DURING PAEDIATRIC CARDIOPULMONARY BYPASS

Authors: D.E. Withington[1] BM, M.E. Elliott[2] MB, W.K. Man[3] PhD

Affiliation: Department of Anaesthesia, St. Thomas' Hospital[1]; Department of Cardiothoracic Surgery, Hospital for Sick Children[2]; Department of Surgery, Royal Postgraduate Medical School[3], London, U.K.

Introduction: Elevated histamine levels have been reported during cardiopulmonary bypass (CPB) in children (1). Possible sources include (i) stored blood used in pump prime, (ii) basophils and (iii) cardiac or lung mast cells. This study investigates the source of histamine released during CPB.

Methods: After Ethical Committee approval twelve children undergoing CPB for correction of congenital heart anomalies were studied. All children received a standard pre-med and inhalational induction of anaesthesia. The extracorporeal circuit was primed with stored blood, Hartmann's solution and mannitol. Cardioplegia was administered after aortic cross-clamping. Patients were cooled to 18°C.
A baseline blood sample was taken immediately before surgery started. Subsequent samples were taken after any event e.g. heparin, start of CPB. After CPB a left atrial (LA) line was placed and parallel samples taken from right atrium (RA) and LA before and 1 and 5 minutes after reventilation. All samples were taken into EDTA on ice. Plasma was frozen at -20°C until assayed by the single isotope radioenzymatic technique (2). Results were compared pre v post event using the Wilcoxon Ranked Pairs Test.

Results: Histamine levels varied considerably between subjects. In 2 children baseline histamine levels were raised but normalised before CPB. In 4 cases histamine rose on initiation of bypass. Histamine levels rose significantly on removal of the aortic cross-clamp ($p < 0.02$) and LA levels were higher than RA levels after reventilation ($p < 0.02$).

Discussion: Histamine release is relevant to CPB because of its cardioactive effects which may be deleterious during CPB.
This study demonstrates an elevation in plasma histamine 3 minutes after aortic cross-clamp removal and a significant elevation in LA over RA levels after reventilation. This suggests that histamine is liberated in the lung vasculature or from right ventricular/left atrial mast cells at the time of reventilation and lung reperfusion. Histamine may thus play a role in intraoperative dysrhythmias and hypotension. The relationship between histamine levels and haemodynamic parameters will be discussed as will the effect of ultrafiltration. The identification of a possible source of histamine during CPB allows for the provision of effective therapeutic intervention.

References:
1. Agents and Actions 20, 299 (1987)
2. Gut 22, 916 (1981)

S326

Title: DOSE-RESPONSE OF ORG-9426 IN CHILDREN DURING NITROUS OXIDE-HALOTHANE ANESTHESIA

Authors: S.K. Woelfel, M.D., B.W. Brandom, M.D., J.B. Sarner, M.D., D.R. Cook, M.D., and J.A. Cyran, Ph.D.

Affiliation: Department of Anesthesiology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania 15213 and Organon Inc., West Orange, NJ 07052

Introduction: ORG-9426 is a steroidal nondepolarizing neuromuscular blocker somewhat less potent than vecuronium with little cardiovascular effect. We determined the dose-response relationship and recovery rate in children during nitrous oxide-halothane anesthesia.

Methods: Thirty-four children (ASA status I-II) between 1 and 5 years old were studied. The study was approved by the hospital's Human Rights Committee; informed consent was obtained from a parent. After induction of anesthesia with nitrous oxide (70%), oxygen (30%), and halothane, an intravenous catheter was placed, atropine (10 µg/kg IV) was given, and the end-tidal halothane concentration was adjusted to 0.8 ± 0.05%. Fentanyl (1-3 µg/kg IV) was given as needed. The ulnar nerve was stimulated supramaximally with repeated trains-of-four stimuli (2 Hz for 2 sec at 10-sec intervals) at the wrist with surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using an NMT monitor. A randomized initial dose of 120, 160, 200, or 240 µg/kg of ORG-9426 was given to each patient. After the maximum effect of the first dose occurred, a second bolus of ORG-9426 was administered over less than five seconds through a T-connector into a rapidly running intravenous infusion to produce a total dose of 300 µg/kg. The initial dose and response from each patient was used to calculate the dose-response relationship (DRR). In 32 patients the DR data from the first two doses was also used to calculate a two-point DRR. DRRs were determined by log-probit transformation of the data and calculation of least squares regression lines. The slopes and ED$_{50}$s determined by each method were compared by t-tests. Time for neuromuscular transmission to return to 10% (T_{10}) and to 25% (T_{25}) function were noted. The recovery index (RI) (T_{10}-T_{25}) was calculated. Standard deviations are shown for all mean values.

Results: The mean age was 37.2 ± 12.6 months; the mean weight was 14.7 ± 2.2 kg (n=34). Two children who received 240 µg/kg had 100% block, and were included only in the total single DRR. There was no difference in slope and ED$_{50}$ between the selected single DR and the two-point DR. However, the slope of the total single DR was statistically significantly different ($p < 0.05$) from that of the two-point DR (Table 1). The RI was 3.4 ± 1.0 min (n=32).

Discussion: ORG-9426 is not more than one-fifth the potency of vecuronium. This suggests that ORG-9426 may have more rapid onset than vecuronium. RI is similar to that of vecuronium (1). Although it is to be expected that the slope of a two-point DR would be less than that produced by the single DR analysis, in this group of 32 children the two-point DR method produces a description of drug potency which is not significantly different from that produced by analysis of only the first dose and response. This is consistent with previous findings of the effects of atracurium in children (2).

Reference:
1. Anesth Analg 62:1083-1088, 1983.
2. Anesthesiology 70:732-736, 1989.

Table 1: Dose-Response Relationship of ORG-9426 in Children

	N	Slope	ED50	R
Total Single DR	34	7.8	165.6	0.77
Selected Single DR	32	6.4	171.4	0.77
Two-Point DR	32	5.8	169.5	

S327

TITLE: INTRAVENOUS CLONIDINE: EFFECT ON THE CARDIOVASCULAR RESPONSE TO INTUBATION

AUTHOR: PMC WRIGHT FFARCS, UA CARABINE FFARCS, E KEARNEY, JP HOWE FFARCS.

AFFILIATION: MATER HOSPITAL AND QUEEN'S UNIVERSITY OF BELFAST, BELFAST, UNITED KINGDOM.

Introduction: Clonidine is a centrally acting α2 adrenergic agonist with antihypertensive properties. It has been recommended for use during general anesthesia because of its cardiovascular stabilising properties[1]. The object of this study is to examine the cardiovascular responses to endotracheal intubation following pretreatment with IV clonidine.

Methods: With ethical committee approval and informed patient consent, sixteen ASA I patients aged 18-55 were pretreated, in a randomised double blind fashion, with either clonidine 1.25 µg kg^{-1} or an equivalent volume of 0.9% saline, 15 minutes prior to induction. Anesthesia was induced with thiopental 3-5 mg kg^{-1} and muscle relaxation achieved with suxamethonium 1.5 mg kg^{-1}. The trachea was intubated and anesthesia maintained with nitrous oxide 66% in oxygen and isoflurane 1% with controlled ventilation until the end of the study period. The ECG was displayed continuously, heart rate (HR bpm) and mean arterial pressure (MAP mmHg) were measured at thirty second intervals throughout the study period using an automated oscillotonometer. Forearm blood flow (FBF ml 100ml^{-1} min^{-1}) and forearm vascular resistance (FVR R units) were also determined at thirty second intervals using mercury strain gauge venous occlusion plethysmography. Measurements were taken for three minutes before the administration of the test drug and continued until 5 minutes following endotracheal intubation. Data are presented as mean ± SD and analysed using multivariate analysis of variance, $P<0.05$ being taken as statistically significant.

Results: Eight patients received clonidine and eight received saline, the two groups were comparable in terms of age, weight, and values for HR, MAP, FBF, and FVR prior to test drug administration. There were no statistically significant differences in the four variables between the groups in the fifteen minute period prior to intubation. Heart rate and mean arterial pressure increased substantially in both groups following intubation but there were no statistically significant differences between the groups. Following intubation forearm blood flow (normal range 3-6 ml 100ml^{-1} min^{-1}) increased in the saline group and decreased in the clonidine group ($P<0.01$ between the groups), forearm vascular resistance decreased in the saline group and increased in the clonidine group ($P<0.05$ between the groups).

	HR	MAP	FBF	FVR
Clonidine	35 ± 11	29 ± 6	-0.5 ± 1.7	28 ± 29
Saline	39 ± 18	35 ± 19	1.9 ± 1.9	-14 ± 24

Table Mean ± SD maximum changes in the four variables after intubation.

Discussion: These results suggest that clonidine 1.25 µg kg^{-1} given 15 minutes before induction does not attenuate the pressor response to intubation. These results also suggest that clonidine will decrease forearm blood flow and increase forearm vascular resistance following intubation compared to a saline placebo.

Reference:
Anesthesiology 67:11-19 (1987).

S328

TITLE: CONTINUOUS FICK CARDIAC OUTPUT MEASUREMENT DURING ANESTHESIA

AUTHORS: T.Yamamura,M.D., K.Sato,M.D., H.Furumido,M.D., O.Kemmotsu,M.D.
AFFILIATION: Dept. Anesth., Hokkaido Univ. Sch. of Med.,Sapporo 060, Japan

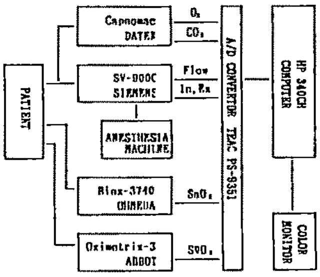
Practical fiberoptic oximetry of mixed venous saturation and arterial pulse oximetry have facilitated to develop a computer based system which monitors cardiac output (CO) by the Fick equation (1). The key part of this system is a respiratory oxygen exchange analyzer. Therefore, we adopted a paramagnetic oxygen analyzer (Capnomac, Datex) and a SV-9000C ventilator (Siemens-Elema) (Fig. 1). The system enabled us to determine CO by breath-by breath basis and to use volatile anesthetics which have been avoided because of their flammability. The system performs on-line compensation for gas transport delay, concentrations of volatile anesthetics and hemoglobin values. The overall accuracy of the system was estimated to be within 5%.

Continuous Fick CO was compared to thermodilution CO in 7 patients anesthetized with enflurane-N_2O-O_2 after institutional approval and informed consent.

A total of 84 simultaneous CO measurements had a range between 3.1 to 10.2 L/min. There was a significant correlation between continuous Fick CO and thermodilution CO with regression coefficient of 0.95 (Fig. 2).

The system also can provide virtually continuous hemodynamic analysis and facilitate more sophisiticated circulatory care of patients within a limited fluctuation.

Reference
Crit Care Med 1986;14:881-885



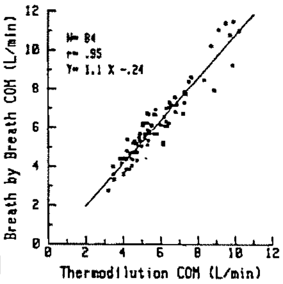


Fig. 1(left) Block diagram of the system for continuous Fick CO measurement.
Fig. 2(right) Scatter plots of continuous breath-by-breath CO and thermodilution CO for 84 paired points.

This study was supported by a Research Grant of Hokkaido University, 1989

S329

Title: EFFECTS OF OPIOID ANESTHETICS ON PORCINE CORONARY ARTERY RESPONSES TO NEUROHUMORAL AGENTS.

Authors: T. Yamanoue MD, J. M. Brum MD, V. Waters MD, C. M. Ferrario MD, F.G. Estafanous MD, P. A. Khairallah MD
Affiliation: Division of Anesthesia, Cleveland Clinic Foundation, Cleveland, Ohio

Introduction: Myocardial ischemia during surgery can be caused by coronary vasospasm (1). Neurohumoral mechanisms may be involved in this phenomenon and various substances have been suggested as possible agents, including acetylcholine (ACh), histamine (HIS) and norepinephrine (NE) (2). Opioid anesthetics, which are widely used seem not to interfere with coronary vasoresponsiveness (3). In this study we investigate the effects of anesthetic doses of fentanyl (3.16×10^{-7} and 3.16×10^{-6} Molar) and sufentanil (3.16×10^{-7} M) on the porcine coronary artery responsiveness to ACh, HIS and NE.

Methods: Left anterior descending coronary arteries were dissected from hearts of adult pigs. The arteries were cut into rings with (E+) and without the endothelium (E-), and prepared for isometric tension studies in physiological saline solution aerated with 95% O_2, 5% CO_2 (pH 7.4 and 37°C). Cumulative dose response curves for ACh, NE and HIS were obtained from experiments done in parallel, on E+ and E- rings, in the presence or absence of opioid anesthetics. Experiments with NE were done in presence of propranolol (5×10^{-6} M).

Results: Fentanyl by itself did not cause any relaxation or contraction of porcine coronary arteries. However, fentanyl reduced ($p<0.05$) ACh-induced contraction in a dose dependent fashion and independently of endothelium (Fig 1). Fentanyl abolished the endothelium-dependent responses to NE (Fig 2). Histamine-induced response was not altered by fentanyl. Sufentanil did not alter ACh induced contraction.

Discussion: Pharmacological responses of porcine and human coronary arteries are similar. In our study, fentanyl diminished muscarinic induced contractions of coronary arteries. This effect, which did not involved the endothelium, suggests that fentanyl anesthesia may alter cholinergic mediated contraction of coronary arteries. Vasoresponsiveness to NE is enhanced in blood vessels without endothelium. We observed that fentanyl abolished the endothelium dependent mechanism of NE induced contraction. Thus, we suggest that fentanyl attenuates NE-mediated effects on smooth muscle and endothelium. These results suggest that anesthesia with high dose of fentanyl may play a role in decreasing the severity of intraoperative coronary vasospasm.

Fig 1

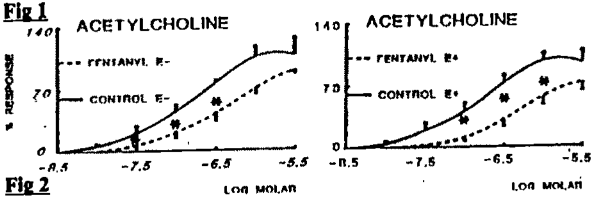
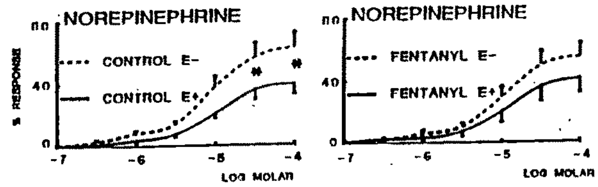


Fig 2



References: (1) J. Mol. Cell Cardiol., 18: 679-689, 1986. (2) Circulation, 69: 430-440, 1984. (3) Anesthesiology, 72: 535-541, 1990

S330

TITLE: EFFECT OF SUCCINYLCHOLINE ON THE RATE AND NATURE OF RECOVERY FROM NONDEPOLARIZING BLOCKADE

AUTHORS: J. T. Yang, B.S.; S.J. Brull, M.D.; J. Turner, M.D.; N.R. Connelly, M.D.; T.Z. O'Connor, M.P.H.; D.G. Silverman, M.D.
AFFILIATION: Anes. Dept., Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510

Introduction: The administration of succinylcholine (SUX) enhances subsequent neuromuscular blockade by a nondepolarizing agent, but the only consistently augmented characteristic is depth of blockade. There are conflicting reports in the literature concerning prolonged recovery from neuromuscular blockade by nondepolarizing agents used following SUX administration.[1,2] Adding to the uncertainty, the effect of SUX on the ratio of the fourth to first twitch (T_4/T_1) of subsequent nondepolarizing blockade has not been determined. Therefore, this study was designed to evaluate the effect of SUX on the rate of recovery and the characteristics of recovery from nondepolarizing neuromuscular blockade.

Methods: With IRB approval, 20 patients undergoing general anesthesia were studied. Peri-induction medication consisted of fentanyl 1-2 mcg/kg and midazolam 0.01-0.02 mg/kg. Surface electrodes from a Digistim III stimulator were placed over the volar forearm, and the ipsilateral thumb was abducted with a tension of 350 gm in an adductor pollicis monitor. Anesthesia was induced with thiopental 4-5 mg/kg, and a baseline train-of-four (TOF) neurostimulation was performed. Intubation was facilitated with one of two muscle relaxant regimens. Group A received SUX 1 mg/kg. Following recovery of T_1 to baseline, vecuronium 0.03 mg/kg was administered. Group B received only vecuronium 0.03 mg/kg. Anesthesia was maintained with 1-2% end-tidal isoflurane, N_2O and O_2. In both groups, TOF was monitored at 10 second intervals following administration of vecuronium. If the depression of T_1 twitch height was not $\geq 80\%$, then supplemental vecuronium was administered in 0.01 mg/kg increments. The time from 25%-75% recovery of T_1 ($T_{25\%-75\%}$) was determined. The T_4/T_1 ratio was quantified at 25%, 50% and 75% recovery of T_1. The groups were compared with respect to their $T_{25\%-75\%}$ (ANOVA) and T_4/T_1 ratios by Wilcoxon rank sum test.

Results: Following SUX the initial vecuronium dose of 0.03 mg/kg always achieved >80% depression of T_1 twitch height. In contrast, in 67% of cases of Group B, at least one supplemental dose of vecuronium was needed. The $T_{25\%-75\%}$ were 746±275 and 603±219 seconds in Groups A and B, respectively ($p>0.05$). As noted in the table, the corresponding T_4/T_1 ratios did not differ significantly.

Discussion: Consistent with most previous investigations, the present data indicate that SUX-induced prolongation of the $T_{25\%-75\%}$ of vecuronium is clinically not significant. The data also indicate that any potential effect of SUX is not reflected by a change in the T_4/T_1 ratio. However, prior administration of SUX did result in more consistent attainment of >80% T_1 depression following 0.03 mg/kg vecuronium. The results suggest that the rate of, and nature of, recovery is essentially unchanged by previous SUX administration.

References
1. Anesthesiology 35:602, 1971
2. Anesth Analg 64:319, 1985

T_4/T_1 RATIOS

	GROUP A	GROUP B
When T_1=25%	6±6	10±9
When T_1=50%	15±10	17±13
When T_1=75%	31±23	28±16

S331

Title: EFFECT OF EPINEPHRINE ON LIDOCAINE INDUCED CONVULSION IN RATS

Authors: M. Yokoyama M.D., W. Ueda M.D.,*
M. Hirakawa M.D.,* H. Goto M.D.,
K. Arakawa M.D., Ph.D
Affiliation: Anes.Dep., University of Kansas, Kansas City, Kansas 66103
*Anes. Dep., Kochi Medical School, Japan

This study was approved by the institutional animal care. The addition of epinephrine to lidocaine has several beneficial effects. However, it is not known what effect epinephrine has on the lidocaine toxicity in the event of accidental intravascular injection. The purpose of this study was to determine if the addition of epinephrine to lidocaine is beneficial or harmful in the event of accidental intravascular injection of a convulsant dose of lidocaine.

Forty awake Wistar rats were divided into 4 groups of 10 each. All groups received a continuous iv infusion of lidocaine (15 mg/ml) at a rate of 0.75 mg/ min until tonic / clonic convulsion occurred. Group 1 received plain lidocaine, Group 2 received lidocaine with 1:200,000 epinephrine, Group 3 received lidocaine with 1:100,000 epinephrine and Group 4 received lidocaine with 1:50,000 epinephrine. Blood pressure and heart rate were continuously recorded and the convulsant dose of infused lidocaine was calculated. Blood samples were withdrawn for determination of blood gases, and plasma concentrations of lidocaine and epinephrine at the onset of convulsion.

The addition of epinephrine decreased the convulsant dose of lidocaine and the higher the concentration of additive epinephrine, the lower the dose of infused lidocaine, as shown in Table1. With respect to plasma concentration of lidocaine at the onset of convulsion, Group 3 and Group 4 showed significant low levels compared with group 1 (Table1). Epinephrine groups produced hypertension, especially Group 3 and Group 4 produced severe hypertension before the onset of convulsion (Fig 1). No group developed severe hypoxia.

Bernards et al. reported the addition of epinephrine (1:200,000) to bupivacaine decreased the convulsant dose of bupivacaine but did not alter the plasma concentration in awake pigs$^{1)}$. Our data showed that not only the calculated convulsant doses of lidocaine but also the measured plasma concentrations of lidocaine were decreased by adding epinephrine. This may be secondary to peripheral metabolic effects of epinephrine and the profound hypertension. Our data suggest that the addition of epinephrine to lidocaine may be harmful in the event of accidental intravascular injection of a convulsant dose of lidocaine.

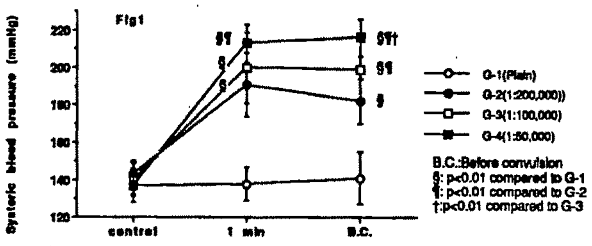
Statistical analysis: ANOVA followed by Duncan's method.

Reference:1) ANESTHESIOLOGY 1989;71:711-717

Table 1

Group (epinephrine conc.)	Lidocaine Dose (mg/kg)	Lidocaine Plasma Conc. (μg/ml)
G-1 (plain)	52.5±5.7	12.5±1.8
G-2 (1:200,000)	41.5±5.8 §	13.1±2.1
G-3 (1:100,000)	30.1±5.6 §¶	9.6±1.9 §¶
G-4 (1:50,000)	22.5±5.5 §¶†	8.8±1.3 §¶

Values are mean ±SD; n=10 §: p<0.01 compared to G-1 ¶: p<0.01 compared to G-2 †: p<0.01 compared to G-3



S332

Title: **Pharmacokinetics of Two-dose Epidural Morphine Regimen for Cesarean Section Analgesia**

Authors: **M. Zakowski MD, S. Ramanathan MD, P. Khoo MD, H. Turndorf MD**
Affiliation: **Department of Anesthesiology, New York University Medical Center, New York, NY 10016.**

Introduction: We have previously shown that two doses of epidural morphine (EM) administered 24 hours apart post cesarean section (CS) eliminate the need for further analgesics[1]. This study compares the pharmacokinetics of the first and the second dose of EM.

Methods: Ten patients gave informed consent after IRB approval. After hydration with 1.5 l Ringer's lactate, epidural anesthesia to a T4 sensory level was induced with lidocaine 2% w/epi 1:200,000. EM 5 mg was administered 1 hr after last lidocaine dose and again 24 hours later. Serum unconjugated and conjugated morphine (UM and CM) were measured 0, .25, .5, 1, 2, 3, 4, 6, 12, 24 hrs after dose 1 and 2. Urine was collected for 3 consecutive 24 hour periods. Serum and urine UM and CM were measured using RIA (range 0.2-200 ng/ml). Area under the curve (AUC), Clearance (Cl), Volume of distribution (VDss), and elimination half-life $t_{1/2}\beta$) were calculated[2]. Results were expressed as mean ± 1 SE and analyzed using t-test at p<.05.

Results: On day 2 serum UM and CM were significantly greater in the first 2 hrs than on Day 1 (Fig). Serum UM Cl significantly decreased while AUC, Vdss, and $t_{1/2}\beta$ were not statistically different (Table). Total urinary excretion of UM (volume*concentration) decreased from 0.37±03 on day 1 to 0.25±.03 day 2 (p<.05) to 0.02±0.002) mg/24hr on day 3 (p<.05). Total CM excretion also decreased from 1.61±0.12 on day 1 to 1.36±0.18 on day 2 (p<.05) to 0.17±0.02 mg/24hr on day 3 (p<.05).

Discussion: The data show that both UM and CM reach higher systemic levels on Day 2 than on Day 1. The decreased serum levels are probably due to increased Cl on Day 1. The increased Cl probably results from increased urinary excretion on Day 1 as evidenced by our data on urinary excretion. Perioperative fluid administration on Day 1 probably accounts for increased urine volume and urinary excretion of morphine on Day 1.

References: 1) Zakowski M, Anesthesiology 1989;71:A833.
2) Shumaker RC, Drug Metab Rev 1986;17:331.

SERUM MORPHINE

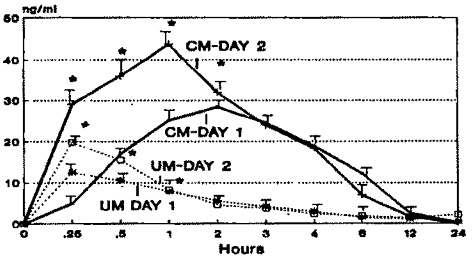


Table Serum morphine pharmacokinetics

	AUC ng-hr/ml	Cl l/hr	VDss l	$t_{1/2}\beta$ hr
Day 1 UM	42±8	139±16	595±80	4±1
Day 2 UM	53±10	100±20*	503±103	5.3±1
Day 1 CM	181±16	30±3.6	121±20	3±0.5
Day 2 CM	193±20	28±3.0	117±21	3±0.5

UM=unconjugated, CM=conjugated, *=p<.05

S333

TITLE: MONITORING OF THE OXYGEN UTILIZATION BY DUAL OXIMETRY DURING AORTIC SURGERY

AUTHORS: U. Zaune, MD, C. Spies, MD, HMF. Pauli, MD, G. Boeden, MD, E.Martin, MD

AFFILIATION: Department of Anesthesiology, Klinikum Nürnberg, D-8500 Nürnberg, W. Germany

The value of dual oximetry has been shown in the treatment of critically ill patients (1-3). Aim of this study was to evaluate the efficacy of dual oximetry in estimating the O_2 utilization coefficient ($O_2UC=VO_2/DO_2$) by monitoring the O_2 extraction index ($O_2EI=[SaO_2-SvO_2]/SaO_2$) during aortic surgery. 60 patients, ASA risk group II-IV, scheduled for abdominal aortic surgery, gave their written informed consent to participate in this institutionally approved study. Before induction of anesthesia hemodynamic monitoring was established with a radial and a fiberoptic pulmonary artery catheter (Hemopro2, Spectramed) for continuous recording of SvO_2 (mixed venous O_2 saturation). SaO_2 (arterial O_2 saturation) was monitored on-line by pulse oximetry (Nellcor 100). Anesthesia and ventilation were standardized. Hemodynamic measurements, analyses of arterial and mixed venous blood samples by an OSM-3 hemoximeter (Radiometer) as well as O_2UC and O_2EI were obtained at T1-T8 (table 1). Statistical analysis was performed by linear regression analysis and bias and precision (b±p).

The results, shown in table 1, demonstrate that, even in critical situations as clamping and declamping of the aorta, O_2EI yields highly significant correlations with O_2UC. Dual oximetry is able to provide simultaneous real-time estimates of pulmonary gas exchange and peripheral tissue oxygen utilization (4), even under the conditions of major vascular surgery. On-line monitoring of O_2EI is able to be reliably used in identifying high risk patients with compromised O_2UC.

Table 1:	O_2UC-O_2EI	b±p
T1=before induction	r=0.797*	+0.1±1.9
T2=post induction	r=0.851*	-2.0±1.8
T3=skin incision	r=0.950*	-1.5±1.4
T4=5'post clamping	r=0.894*	-1.7±2.1
T5=15'post clamping	r=0.674*	-2.1±3.5
T6=5'post declamping	r=0.707*	-0.9±4.7
T7=15'post declamping	r=0.812*	-1.5±2.5
T8=skin closure	r=0.933*	-2.0±1.7

*:$p \leq 0.0001$

References:

1. Räsänen J et al (1987) Ann Surg 207:621
2. Nelson LD (1990) In: Vincent JL (ed) Update 1990, vol.10, Springer, Berlin, 431
3. Downs JB (1990) In: Vincent JL (ed) Update 1990, vol.10, Springer, Berlin, 440
4. Räsänen J. et al (1988) Intensive Care Med14: 118

S334

TITLE: BUPIVACAINE TOXICITY IN SPONTANEOUSLY HYPERTENSIVE RATS

AUTHORS: F. Zavisca, M.D., J. Heavner, Ph.D., J. Kytta, M.D., P. Rosenberg, M.D., C. Iacono, Ph.D., M. Badgwell, M.D.

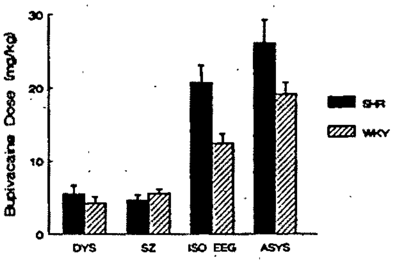
AFFILIATION: Anes. Depts. TTUHSC, Lubbock, TX and University of Helsinki, Finland

Hypertension is associated with a number of changes that might modify toxic response to bupivacaine. For instance, animals with hypertension have increased susceptibility to seizures and increased propensity for cardiac arrhythmias.[1,2] The toxicity of bupivacaine in spontaneously hypertensive rats (SHR/n=6) and Wistar Kyoto rats (WKY/n=6) was compared. After institutional approval, the animals were anesthetized with halothane. Following tracheal and vessel cannulation, pancuronium 0.1 mg/kg was given IV and mechanical ventilation with 70% N_2O, 30% O_2 and 0.5% halothane was started. Bupivacaine infusion at 2 mg/kg/min IV produced ventricular dysrhythmias (DYS); seizures (SZ); isoelectric EEG (ISO EEG); and asystole (ASYS). Doses producing these endpoints were compared by analysis of variance. Doses producing DYS and SZ were not significantly different from each other within each group, nor between SHR and WKY (fig.). The dose producing ISO was greater in the SHR ($p<0.05$), and greater than the dose producing SZ in both strains ($p<0.05$). The seizure period was significantly longer in the SHR (8.0 ± 1 min) than in the WKY (4.5 ± .6 min) ($p<0.05$). Doses producing ASYS were slightly though not significantly greater in the SHR ($p>0.05$), and greater than the dose producing ISO EEG in both strains ($p<0.05$). Mean blood pressure (MBP) was higher in the SHR at most endpoints ($p<.05$). Maintenance of a higher brain perfusion pressure and/or an alteration of brain response to bupivacaine with SHRs may account for the prolonged seizure period in this strain of rats.

References:

1. Greenwood, R.S. et al: Brain Res 495 (1989) 58-65
2. Cameron J.S. et al: Eu J Pharmacol 169 (1989): 23-31

DOSES OF BUPI. FOR SHR & WKY AT TOXIC ENDPOINTS + S.E.



S335

TITLE: INTRAOPERATIVE ALFENTANIL PCA: COMPARISON WITH STANDARD BOLUS AND INFUSION TECHNIQUES

AUTHORS: J. Zelcer, MD, P.F. White, PhD, MD, J.P. Paull, MD, S. Chester, MD
AFFILIATION: Departments of Anesthesiology, Royal Women's Hospital, Melbourne, Australia, and Washington University, St. Louis, MO 63110

Opioid analgesics are commonly used adjuvants for improving patient comfort during surgical procedures performed under monitored anesthesia care (MAC). The perioperative effects of alfentanil when administered using a patient-controlled analgesia (PCA) delivery system was compared to a continuous infusion or intermittent bolus technique during MAC for vaginal ovum pickup (VOPU). This IRB-approved study was designed to determine opioid requirements, cardiorespiratory effects and clinical acceptability of these three modes of analgesic administration.

51 healthy, consenting adult outpatients presenting for VOPU were randomly assigned to receive alfentanil via PCA (P), continuous infusion (I), or intermittent bolus (B) injection. All outpatients were premedicated with midazolam, 0.02 mg/kg iv. Following a standard loading dose of alfentanil, 15 ug/kg iv, Group P self-administered bolus doses of 5 ug/kg iv, on demand using a Graseby PCA device; Group I received an initial infusion rate of 1.0 ug/kg/min, which was subsequently varied by the anesthesiologist; and Group B received alfentanil, 5 ug/kg iv, bolus doses according to the clinical judgment of the anesthesiologist. Data were analyzed with a Kruskal-Wallis ANOVA, $p < 0.05$ was considered significant (means ± S.D.).

The three groups were similar with respect to age, weight, and duration of procedure. Alfentanil dosage requirements were 2018 ± 171, 1644 ± 110, and 1504 ± 126 ug in Groups P, I, and B, respectively. Intraoperative heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), oxygen saturation ($Sa0_2$), and end-tidal $C0_2$ ($ETC0_2$) values were unchanged from baseline values (table 1). Additionally, there were no significant differences between groups in recovery times, intraoperative pain scores, or postoperative emetic sequelae. All patients in the PCA group who had previously undergone a VOPU with physician-controlled analgesia expressed a preference for controlling their own intraoperative pain medication.

In conclusion, all three techniques for administering alfentanil during MAC were safe and effective. Similar doses of alfentanil were administered in both the patient and physician-controlled groups. Thus, PCA would appear to be an attractive alternative to physician-administered analgesia during MAC.

Table 1: Cardiorespiratory variables during VOPU procedures*

	PCA (P)				Infusion (I)				Bolus (B)			
Time (min)	0	5	10	15	0	5	10	15	0	5	10	15
HR (BPM)	89	86	83	84	80	76	77	76	81	80	79	79
MAP (torr)	94	89	89	90	96	90	91	89	101	96	94	96
RR (BPM)	18	17	17	18	17	17	17	17	17	16	17	17
$ETCO_2$ (torr)	33	40	42	42	36	39	39	38	35	39	37	40

*With supplemental 0_2 (2 L/mm NP), all $Sa0_2$ values were 100%

S336

TITLE: SPREAD OF HYPERBARIC (HBS) AND ISOBARIC (IBS) SOLUTIONS: NEEDLE VS. CATHETER IN SUBARACHNOID SPACE MODEL (SASM)

AUTHORS: R.F. Erian, M.D., D. Levin, W.J. Hwang
AFFILIATION: Dept. Anesth., Univ. Texas Health Science Center, San Antonio, TX 78284-7838

Introduction: It was our clinical impression that the spread of local anesthetics injected into the subarachnoid space using a needle or an epidural catheter were different. We, therefore, compared the spread of an intrathecal injection of hyperbaric and isobaric solutions using three modes of injection in a subarachnoid space model (SASM).

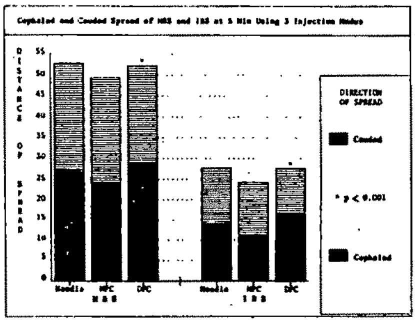
Methods: The SASM consisted of Tygon tubing (1/2" ID, 66 cm long) filled with normal saline. Injected solutions were: 1:1 dilution of 0.75% methylene blue (2 ml) with either Dextrose 10% (HBS) or normal saline (IBS). Solutions were maintained at room temp and injected using a 3 ml syringe. Specific gravities of the solutions were measured at room temp. Injections were made through a 25 g spinal needle, a 20 g multiport (mpc) and 20 g distal port (dpc) epidural catheters inserted in the horizontal plane. Epidural catheters were inserted 3 cm into and parallel to the SASM lumen, whereas the needle was inserted 0.5 cm and perpendicular to the lumen. Both the tip of the needle and that of the catheter were mid-point from the ends of the SASM. Spread was measured from the mid-point in both directions. The direction facing the needle bevel or the catheter tip is referred to as cephalad. Each solution was injected 5 times using the 3 different techniques. Spread was measured at 1, 2, 3, and 5 min from injection time, with 5 min data presented as the mean and standard deviation. Comparisons were made using a paired students t test, $p < 0.05$ was considered statistically significant.

Results. The specific gravities of normal saline, methylene blue 0.75%, dextrose 10%, HBS and IBS were 1.007, 1.002, 1.024, 1.018 and 1.006, respectively. See figure for spread of solutions.

Discussion: Cephalad and caudad spread of both solutions at 5 min is symmetrical using a 25 g spinal needle or a 20 g mpc, but not with a 20 g dpc. With the dpc, cephalad spread is more than 5 cm greater than in the caudad direction with both solutions at 5 min ($p<.001$). Total spread is similar for both needle and dpc and less for mpc with both solutions. Spread was almost 2-fold greater with HBS than IBS, independent of the injection technique used ($p<.001$).

Conclusion: Cephalad spread with both HBS and IBS is greater than caudad spread using a dpc and would represent clinically at least 2 segments more. Since the catheters are inserted typically at a L3-L4, the high point of the spinal curvature in the supine position, this difference in spread could be greatly accentuated by gravity. These results suggest that a bolus injection of local anesthetics via a dpc would be associated with a much higher level of spinal anesthesia than anticipated. Consequently, a careful titration should be used, especially when using a HBS where the total spread is much greater.

Reference
1. Anesth Analg 64:715-730, 1985
2. Res Staff Phys, pp. 79-87, Sept. 1987.



Author Index

Abdel-Latif M, Kim S-J, Salem MR, Crystal GJ. Phenylephrine does not limit myocardial O_2 delivery during isoflurane-induced hypotension in dogs, S1
Adriaensen H, see Vercauteren M
Aho M, Lehtinen A-M, Erkola O, Korttila K. A novel α_2-agonist, dexmedetomidine as intramuscular premedication for laparoscopy, S2
  see Lehtinen A-M
Alagesan R, see Kross R
Albala D, Coombs D, Colburn R, Del Guidice P. Temporal correlation between toxic plasma & urinary inorganic fluoride levels and urinary PGE2 in the ewe, S3
Albanese MA, see From RP
Albrecht RF
  see Cheng MA
  see Hoffman WE
Ali HH, Goudsouzian NG. Effect of succinylcholine on plasma potassium, elderly vs. young, S4
  see Shorten GD
Ali J, see Cohen E
Alon E, see Atanassoff PG
Amberger M, see Tolksdorf W
Anderson EP, see Stensrud PE
Anderson JA, see Blau WS
Antiporda C, see Patel N
Aoki H, see Inada E
Aoki K, see Inada E
Apfelbaum J, see Meyer P
Apfelbaum JL, Lichtor JL, Lane B, Coalson DW, Uitvlugt A, Rupani G, Schreider B, Glosten B, Roizen MF, Finn R. Rates of awakening from desflurane or propofol in human volunteers, S5
  see Lichtor JL
Arakawa K
  see Ohara S
  see Yokoyama M
Aronson S, see Lin CY
Atallah MM, see Saied MMA
Atanassoff PG, Alon E, Biro P, Schawalder J, Pasch T. Recovery after propofol, midazolam, and methohexital as an adjunct to epidural anesthesia, S6
Atlee JL, see Laszlo A
Azad SS
  see Bartkowski RR
  see Lessin JB
  see Rosenblum F
Azuma K, see Fujiwara Y

Babu S, see Shibutani K
Badgwell JM, see Heavner J
Badgwell M, see Zavisca F
Badner NH, Murkin JM, Lok P. Differences in pH management and pulsatile/nonpulsatile perfusion during cardiopulmonary bypass do not influence renal function, S7
Baele PL, Housmans PR. Effects of halothane, enflurane and isoflurane on the ferret cardiac length-tension relation, S8
Baker AJ, Zornow MH, Grafe MR, Scheller MS, Yaksh TL, Larson AA, Shapiro HM. Effects of hypothermia on neurologic outcome and brain glutamine levels following ischemia in rabbits, S9
Baker T
  see Handlin DS
  see Patel N
Banner MJ, Kirby RR, Blanch PB. Site of pressure measurement during CPAP: effect on calculating imposed work of breathing, S10
  see Rodes WD II
Barker SJ, Clarke C, Hyatt J, Le N, Bhakta C. Thoracoscopic laser ablation of bullous emphysema: an anesthetic case study, S11
Barnes A, see Furgerson C
Baron MJ, Gunter JB, White PF. Is the hematocrit needed prior to outpatient pediatric surgery?, S12
Bartkowski R, see Rosenblum F
Bartkowski RR, Azad SS, Witkowski TA, Seltzer JL. Hemodynamic responses to desflurane (1653) anesthesia: a comparison with isoflurane, S13
  see Lessin JB
  see Schieren H
Bates MF, see Kraynack BJ
Battito MF, Langner R, Bradley EL. Desflurane and alfentanil in surgical outpatients: comparative hemodynamics, emergence, and recovery, S14
Baxter AD, see Sandler AN
Beattie RB, see Orr DA
Beattie WS, Forrest MB, Buckley DN. Comparison of perioperative ischemia to ischemic attacks in non-surgical patients, S15
Beaver B, see Fisher Q
Beck GJ, see Higgins T
Bedford R, see Jain S
Bedford RF, see Gatell JA
Bednarski M, see Licina MG
Bell SD. Characteristics of acute respiratory depression seen with epidural fentanyl, S17
  The correlation between pulmonary function and resting and dynamic pain scores in post aortic surgery patients, S18
Bennett HL, see Dwyer R
Bennett JA, Lingaraju N, Keykhah MM, McElrath T, Damask M. Comparati effects of desflurane and isoflurane the elderly, S19
Bennetts P, see Kovac A
Benthuysen J, see Soriano S
Berens RJ, see Ebert TJ
Bernstein D, see Rosenberg AD
Berquist TH, see Jorgensen NA
Berry A, see Sneyd JR
Bevacqua BK, Slucky AV. Intrathecal lidocaine/fentanyl infusion for pos operative analgesia, S20
Beynen FM, see Nuttall GA
Bhakta C, see Barker SJ
Biglan A, see Cheng K
Bill KM, see Orr DA
Bires J, McGregor D, Lennon R. Reversal deep neuromuscular blockade with low dose neostigmine in infants an children, S21
  see McGregor D
Biro P, see Atanassoff PG
Bissell DM, see Kelley SD
Bissonnette B
  see Leon J
  see Sloan M
Black D, see Flanagan JF
Blanch PB, see Banner MJ
Blau WS, Kafer ER, Anderson JA. Esmolol superior to nitroprusside for controlled hypotension during oral surgery, S22
Bloomfield E, see Schubert A
Blum J, see Higgins T
Blum JM, see Licina MG
Boban M, Stowe DF, Goldberg AH, Buljubasic N, Kampine JP, Bosnjak ZJ. 2,3 Butanedione monoxime improves function and rhythm afte hypoperfusion in isolated guinea pi hearts, S23
  see Buljubasic N
  see Mehner RW
Boban N, see Schedewie HK
Boeden G
  see Spies C
  see Zaune U
Bogetz MS, Vessey JA, Caserza CL. Parent upset caused by participating in the child's anesthetic induction, S16
Boltz G, see Fisher Q
Bosnjak ZJ
  see Boban M
  see Buljubasic N
  see Eskinder H
  see Flynn N
  see Laszlo A

  see Mehner RW
  see Schedewie HK
  see Stadnicka A
  see Stowe DF
  see Supan F
  see Tudoric N
  see Turner LA
Boucaud C, Lichtor JL, Emond J, Broelsch C, Erickson J, Polk S, Rupani G. Blood loss during liver transplantation: 1984-1990, S24
  Lichtor JL, Emond J, Broelsch C, Erickson J, Polk S, Rupani G. Thromboelastography during liver transplantation: does blood loss correlate with abnormalities?, S25
  Polk A, Glusman S. Aminophylline accelerates recovery from fatigue in rat isolated diaphragm by acting on adenosine receptors, S26
Bowdle TA, see Freund PR
Boylan J, see Teasdale S
Boylan M, see Heavner J
Boylen P, see Cheng DCH
Bradley EL, see Battito MF
Bradley EL Jr
  see Jebeles JA
  see Vinik HR
Brandom BW, see Woelfel SK
Braverman B
  see Fischer R
  see Sosis M
Brems J, see Tetzlaff JE
Brody MC, Wheeler DS, Stacey BR, Burke DF, Dunwoody C. Increased analgesia requirements in patients using PCA narcotics for post operative analgesia, S27
Broelsch C, see Boucaud C
Brooks DE, see Snodgrass GW
Brosstad R, see Kongsgaard UE
Brull SJ, Connelly NR, Silverman DG. Comparison of crystalline skin temperature to esophageal, pulmonary artery, and bladder temperature during cardiopulmonary bypass, S28
  Lieponis J, Murphy M, Silverman DG. Iliac crest wound perfusion for postoperative analgesia, S29
  see Silverman DG
  see Yang JT
Brum JM, see Yamanoue T
Buckley DN, see Beattie WS
Budzilovich G, see Wang BC
Buljubasic N, Marijic J, Boban M, Stowe DF, Bosnjak ZJ. Effects of enflurane on global ischemia and reperfusion in isolated guinea pig hearts, S30
  see Boban M
  see Mehner RW
  see Supan F
Burgess FW, see Snodgrass GW
Burke BE, see Layon AJ
Burke DF, see Brody MC
Burt ME, see Gatell JA
Byrne BA, see Howie MB

Cahalan MK, see Muhiudeen IA
Caldwell JE
  see Segredo V
  see Szenohradszky J
Calkins J, see Kovac A
Campbell R, see Nakatsuka M
Camporesi E, see Mangar D
Cantley E
  see Kwan W-F
  see Tsai SK
Capogna G, Celleno D, Constantino P, Sebastiani M, Muratori F, Cipriani G. A comparison of morphine and buprenorphine via P.C.A. plus basal infusion in postcesarean delivery patients, S31
Carabine UA, see Wright PMC
Carp H, see Milligan KR
Carton EG, Housmans PR. Role of transsarcolemmal Ca2+ entry in the negative inotropic effect of nitrous oxide in isolated ferret ventricular myocardium, S32
Caserza CL, see Bogetz MS
Casey WF, see Mostello LA
Celleno D, see Capogna G
Chabal C, see Jacobson L
Chan V, see Chung F
Chandler LH, White PF. Ambulatory PCA -a new approach to postoperative pain management, S33
Chaney E, see Jacobson L
Chang P, Johnson D, Hurst T, Reynolds B, Lang S, Mayers I. Changes in end-tidal CO_2 with bronchial occlusion and one lung canine ventilation, S34
Chantigian RC, Danilenko-Dixon DR. Epidural analgesia, instrumental vaginal delivery and the primiparous parturient, S35
Charles D, see Williamson WK
Chaundhry I, see Foldes FF
Chen B-J
  see Kwan W-F
  see Tsai SK
Chen BJ, see Kwan WF
Chen L, see Fisher SM
Cheng DCH, Feindel CM, Cruz J, Boylen P, Ong D. Effects of metoprolol and nifedipine on post-ischemic regional myocardial blood flow in a chronic swine model, S36
Cheng EY, Kampine JP. Anesthetic drugs and nonanesthesiologists, S37
Cheng K, Biglan A, Larson C, D'Antonio J. A comparison of retrobulbar and general anesthesia for strabismus surgery, S38
Cheng MA, Hoffman WE, Miletich DJ, Albrecht RF. Clonidine improves neurologic outcome following incomplete ischemia in rats, S39
Chester S, see Zelcer J
Christie JM, Jones CW. Mass spectroscopic/gas chromatograph analysis of drug combinations for regional anesthesia, S40
  Leon M. Work of breathing and pressure support ventilation during general anesthesia, S41
Chu FC, see Watcha MF
Chuah EC, see Kwan WF
Chung F, Ong D, Seyone C, Mati N, Powell P, Chan V. A new postanesthetic discharge scoring system for ambulatory surgery, S42
Cioffi A, see Rosenblatt W
Cipriani G, see Capogna G
Clark SK, see Rung GW
Clarke C
  see Barker SJ
  see Keaveny J
Coalson D
  see Lichtor JL
  see Meyer P
Coalson DW
  see Apfelbaum JL
  see Dohrn CS
Cochran P, see Gulden RH
Code WE, see Rooney ME
Cohen E, Salter O, Ali J. Effect of incremental PEEP on PaO_2 and SVO_2 during OLV, S43
Cohen S, Mathews D, Weissman C. ST segment analysis during deliberate hypotension, S44
Cohn M, see Cohn ML
Cohn ML, Machado AF, Cohn M. Back pain therapies: objective, reproducible outcome determination, S45
Colburn R, see Albala D
Colclough G, see Walmsley PNH
Cole DJ, see Schell RM
Connelly NR
  see Brull SJ
  see Yang JT
Conrad P, see Weller RS
Constantino P, see Capogna G
Cook DJ, Housmans PR. Mechanism of the positive inotropic effect of ketamine HCl in isolated ferret ventricular myocardium, S46
Cook DR
  see Gronert B
  see Woelfel SK
Cook R
  see Mulroy JJ
  see Welborn L
Coombs D, see Albala D
Coon RL, see Tudoric N
Corey E, see Spiess BD
Corey ER, see Parnass SM
Correa-Sales C, Guo T-Z, Yaksh TL, Maze M. Dexmedetomidine, an α_2 adrenergic agonist, exerts a biphasic anesthetic and analgesic response in the rat C.N.S., S47

Coté C, see Welborn L
Cotev S, see Shapira Y
Cramp P, see Milligan KR
Crawford ES, see Shenaq SA
Crosby G, see Szabo MD
Cruz J, see Cheng DCH
Crystal GJ, Kim S-J, Czinn EA, Salem MR, Mason WR. Intracoronary isoflurane causes marked vasodilation in canine hearts, S48
  see Abdel-Latif M
Csete Prager M, see Kelley SD
Cyran JA, see Woelfel SK
Czinn EA, see Crystal GJ

Daley MD, see Norman PH
Dalisan J, see El-Naggar M
Damask M, see Bennett JA
Damask MC, see Ebrahim Z
Dan K, see Tanaka K
Danilenko-Dixon DR, see Chantigian RD
D'Antonio J, see Cheng K
Davis P, see Welborn L
Davis PJ
  see Gronert B
  see Mulroy JJ
Day AL, see Mahla ME
de Sousa H, see Mangar D
Deegan R, He HB, Wood AJJ, Wood M. Propofol markedly inhibits sympathetic activity: assessment of NE kinetics in dogs, S49
Del Guidice P, see Albala D
DeLisser EA
  see Helfman SM
  see McMillan DW
Dewan JA, see Shafer AL
deWit H, see Dohrn CS
Diaz J, see Matteo RS
Dinner M, see Welborn L
Dionne R, see Meyer P
Dobkowski WB, Murkin JM, Sharpe MD, Molotiu N, Guiraudon G, Yee R. The effect of enflurane (1 MAC) on the normal AV conduction system and accessory pathways, S50
  see Moote CA
  see Sharpe MD
Dohrn CS, Zacny JP, Lichtor JL, Finn RS, Coalson DW, deWit H. Subjective effects of nitrous oxide in normal volunteers, S51
Dozaki S, Okamura A, Morimoto Y, Komura Y, Kaseno S, Kemmotsu O. Controlled hypotension by prostaglandin E1 in normotensive and hypertensive patients, S52
  Okamura A, Yamamura T, Kemotsu O. Analysis of renal function during controlled hypotension with PGE1, TNG or TMP in humans, S53
Dretchen KL, see Fleming NW
Duarte JA, see Howie MB
Dubbink DA, Rettke SR, Sittipong R, Krom RAF. Preoperative pseudocholinesterase levels as an indicator of intraoperative blood usage in patients undergoing orthotopic liver transplantation, S55
  Rettke SR, Williamson KA, Sittipong R, Krom RAF. Calcium chloride requirements versus fresh frozen plasma transfused during orthotopic liver transplantation, S56
Dubois M, Kataria B, Lea D, Lapeyre G. Neuromuscular effects of ORG-9426 in humans during general anesthesia with and without enflurane, S57
Duke P, see Meyer P
Dull JJ, see Nuttall GA
Dunwoody C, see Brody MC
Durbin CG Jr, Kopel RF, Orsina A. ICU readmissions: do they reflect premature discharge?, S58
  Smith W, Orsina M. Should CPR be withheld from the chronically ill and elderly?, S59
Durkan WJ, see Leicht CH
Durkin M, see Rafferty T
Dworkin R, see Handlin DS
Dwyer R, Bennett HL, Peterson N, Eger EI II. Can unconscious learning occur during isoflurane anesthesia?, S60

Ebert TJ, Berens RJ, Muzi M, Kampine JP. Direct comparison of etomidate & propofol on sympathetic neural outflow & baroreflex function in man, S61
Ebrahim Z, O'Hara J, Tetzlaff J. Should monoamine oxidase inhibitors be discontinued preoperatively?, S62
  Schoenwald P, Grimes-Rice M, Damask MC, Khairalah PA. Multiple dose evaluation of the efficacy of ocfentanil HCl (A-3217) to produce postoperative analgesia, S63
Ebrahim ZY, see Schubert A
Eger EI II, see Dwyer R
Eick C, see Tolksdorf W
Ekerle JS, see Kemmotsu O
El-Baz N, Faber L, Kittle F, Warren W. Single-lumen tube for two-lung and one-lung ventilation during thoracic surgery, S64
El-Kenawy M, see Saied MMA
El-Naggar M, Mathew M, Dalisan J, Kartha R. The effect in the parturients of epidural catheters, lidocaine test dose and fentanyl, S65
Elefteriades J, see Rafferty T
Elliott ME, see Withington DE
Elmore J, see Gulden RH
Emond J, see Boucaud C
Engelman E, see Van der Linden P
Ereth MH, Sessler DI, Lennon RL. Isolation of peripheral and central thermal compartments in vasoconstricted postoperative patients, S66
  Stensrud PE. Spinal cord imaging with transesophageal echocardiography, S67
Erian RF. Phrenic artery blood flow during single twitch stimulation of the dog diaphragm, S68
  Levin D, Hwang WJ. Spread of hyperbari (HBS) and isobaric (IBS) solutions: needle vs. catheter in subarachnoid space model (SASM), S336
Erickson J, see Boucaud C
Erkola O, see Lehtinen A-M
Eskinder H, Supan F, Turner LA, Kampine JP, Bosnjak ZJ. Effect of halothane o slowly inactivating Na+ current in canine cardiac Purkinje cells, S69
  see Supan F
Estafanous FG
  see Higgins T
  see Licina MG
  see Yamanoue T
Evans DE, see Leicht CH
Everts E, see Pilato MA
Exler J, see Roa NL

Faber L, see El-Baz N
Fahmy NR, Patel D, Sunder N. Pulmonary and systemic hemodynamics, ECG and blood gas changes with use of a pneumatic tourniquet, S70
Falinksi B, Klochany A, Sebel PS, Hug CC J Hemodynamic effects of pentamorphone for cardiac anesthesia, S71
Farrugia R, see Pilato MA
Fawcett W, see Ravalia A
Fee JPH, see McKinney MS
Feindel CM, see Cheng DCH
Ferguson RL, see Hoffman WE
Ferlazzo P, see Shibutani K
Ferrario CM, see Yamanoue T
Finn R
  see Apfelbaum JL
  see Lichtor JL
  see Lin CY
Finn RS, see Dohrn CS
Fischer R, Braverman B, McCarthy R, Ivankovich A. Nicardipine augment cardiovascular hemodynamics during deliberate hypotension in dogs, S72
Fisher D, see Welborn L
Fisher Q, Spurrier E, Boltz G, McComiskey C, Beaver B, Hill J. Does addition of epinephrine delay voiding or enhance caudal analgesia in children?, S73
Fisher SM, Mickler TA, Chen L, Plate JF. Patient outcome and anesthesia care during semi-emergent intubations outside the operating room, S74
Flanagan JF, Kumatta D, Black D. Comparison of 24 gauge Sprotte and 27 gauge Quincke needle on the incidence of post dural puncture headache, S75

Fleming NW, White DA, Lewis BK, Dretchen KL. Acute effects of calcitonin gene-related peptide on neuromuscular function, S76
Fletcher J, see Sebel PS
Fletcher JE, Sebel PS, Mick SA, Van Duys J, Ryan K. Pharmacodynamic comparison of vecuronium and atracurium, S77
  Sebel PS, Murphy MR, Smith CA, Flister MP, Mick SA. Psychomotor recovery after desflurane in outpatients, S78
Flister MP, see Fletcher JE
Flynn N, Bosnjak ZJ, Kampine JP. Volatile anesthetic effect on serotonin induced vasomotion in isolated canine cerebral arteries, S79
  see Stadnicka A
Foldes FF, Chaundhry I, Nagano O, Ohta Y, Vizi ES. Mechanism of the inhibition of neuromuscular transmission by adenosine in mice, S80
  see Vizi ES
Forbes GS, see Jorgensen NA
Forbes RB, see Murray DJ
Forrest JB, see Beattie WS
Franklin C, see MacDonald LE
Franklin CM, see Fukuoka RH
Freund PR, Bowdle TA, Neuenfeldt T, Posner K. Reversal of intraoperative pulse oximetry failure by digital nerve block, S81
From RP, Kreiter CD, Albanese MA, Pearson KS, Moyers JR, Gomez M, Hindman BJ, Murray D, Tinker JH. Academic performance and personality traits: influence on PGY-I applicant selection, S82
Fujimaki K, see Fujiwara Y
Fujita Y, Hamada H, Kimura K, Takaori M. Protective effect of nicardipine against hypoxic injury in the isolated, perfused rat liver, S83
Fujiwara Y, Fujimaki K, Mike N, Azuma K, Shimada Y, Naoe T. Halothane and proto-oncogene 'c-myc' expression, S84
Fukunaga AF, see Kaneko Y
Fukuoka RH, Kelly JW, Franklin CM. Correlation between ETT size, distal digit diameter and the Penlington formulae, S85
Fung D, see Soriano S
Furberg C, see Stump DA
Furgerson C, Barnes A. Residency program criteria for completion of clinical competence reports, S86
Furumido H, see Yamamura T
Furuta S, see Inada E

Galbraith TA, see Howie MB
Gallagher TJ, see Layon AJ
Gatell JA, Burt ME, Bedford RF, Reinsel R. Does isoflurane anesthesia affect growth of methylcholanthrene-induced rat sarcoma?, S87
Geiran O, see Konsgaard UE
Gelb AW
  see Gignac EA
  see Manninen PH
Gennings C, see Hudson JC
Getson P, see Norden J
Ghouri AF, White PF. Comparative effects of desflurane and isoflurane on neuromuscular function, S88
  White PF. Effect of desflurane on vecuronium-induced neuromuscular blockade, S89
Gibbs N, Harrison B. Profound neuromuscular blockade does not reduce the hemodynamic response to tracheal intubation in man, S90
Gignac EA, Manninen PH, Gelb AW. The comparison of the use of three narcotics during awake craniotomy, S91
  see Manninen PH
Gilbart E, see Van der Linden P
Gillis J, see Pilato MA
Glosten B
  see Apfelbaum JL
  see Lichtor JL
Glusman S, see Boucaud C
Godbey PS, see Hillier SC
Gold MI
  see Helfman SM
  see McMillan DW
Goldberg AH, see Boban M
Goldberg ME, see Schieren H
Gomez M, see From RP
Goto H
  see Ohara S
  see Yokoyama M
Goto K, see Ohara S
Goudsouzian NG, see Ali HH
Grafe MR, see Baker AJ
Gramsch C, see Stein C
Grant GJ, Ho I, Winter E, Ramanathan S, Turndorf H. Epidural versus intravenous fentanyl during cesarean section, S92
Gravenstein N
  see Lampotang S
  see Rhodes WD II
Gray J, see Jorgensen NA
Greenblatt D, see Pilato MA
Grimes-Rice M
  see Ebrahim Z
  see Schubert A
Grogono AW, see Meyer P
Gronert B, Davis PJ, Cook DR. Continuous infusions of alfentanil in infants under one year of age undergoing inguinal herniorrhaphy, S93
Gronert G, see Meyer P
Gross JB, see Weller RS
Gruenke LD
  see Segredo V
  see Szenohradszky J
Grun JL, see Maurer PM
Grundy BL
  see Mahla ME
  see Pashayan AG
Grunwald Z, Schieren H, Torjman M. Pharmacokinetics of droperidol in children, S94
Guertin MG, see Howie MB
Guiraudon G
  see Dobkowski WB
  see Sharpe MD
Gulden RH, Whitten CW, Latson T, Lipton JM, Cochran P, Elsmore J. Radiant heat reduces requirement for vasodilator drugs after cardiopulmonary bypass, S95
Gunter JB, see Baron MJ
Guo T-Z, Tinklenberg J, Oliker R, Maze M. Central α_1 adrenoceptor stimulation functionally antagonizes the hypnotic response to dexmedetomidine, an α_2 agonist, S96
  see Correa-Sales C
Gutierrez JF, see Jebeles JA
Gyermek L, Nguyen N, Lee C. Muscarinic receptor subtype selectivity of tropacocaine derivatives in the rat, S97

Haas GS, see Mihiudeen IA
Hager RA, see Stein CS
Haisty WK, see Olympio MA
Hakim TS, see Presson RG Jr
Hall RI, Murphy JT, Moffitt EA, Landymore RW, Maritime Heart Centre. Propofol-sufentanil vs. enflurane-sufentanil anesthesia in cardiac surgical patients: hemodynamics, S98
  see Murphy JT
Hamada H, see Fujita Y
Handlin DS, Baker T, Dworkin R, Richlin D. Role of nerve block and effect of pain duration in a chronic pain population, S100
  Baker T. The effect of heavy and light smoking on patient duration in the post anesthesia care unit, S99
Hanis C, see Khalil S
Hannallah R
  see Norden J
  see Welborn L
Harada K, Yamamura T, Okamura A, Kemmotsu O. Synaptic mechanisms of halothane anesthesia, S101
Harris TL, see Podraza A
Harrison B, see Gibbs N
Hartman JC, see Warltier DC
Haselby KA, see Hillier SC
Haskins DA, Jahr JS, Ramadyhani U, Texidor M, Kelley D. Does omeprazole, a gastric acid pump inhibitor reduce gastric volume and acidity in outpatients?, S102
Hassan AHS, see Stein C
Hayes SR, see Vogelsang J
He HB, see Deegan R

Heavner J, Zavisca F, Badgwell JM, Boylan M, Rosenberg P. Cardiovascular and central nervous system effects of bupivacaine in magnesium deficient rats, S103
  see Zavisca F
Heidelmeyer CF, Schroeder T, Hering JP, Veit S, Hellige G. Loss of cardiac effectivity with catecholamines in hypothermia - three distinct mechanisms in sheep, S104
Helfman SM, Gold MI, DeLisser EA, Herrington C. A comparison of lidocaine, fentanyl and esmolol in the prevention of intubation related tachycardia and hypertension, S105
Hellige G, see Heidelmeyer CF
Hennes HJ, Jantzen JP, Dick W. Effects of fenoldopam on cerebral autoregulation and CO_2-reactivity in swine, S106
  see Jantzen J-P
Hering JP, see Heidelmeyer CF
Heropoulos M, see Schieren H
Herrington C, see Helfman SM
Herz A, see Stein C
Hickey R, see Sloan TB
Higgins T, Estafanous FG, Loop FD, Blum J, Beck GJ. Evaluation of operative risk in patients undergoing coronary artery bypass grafting, S107
Hill J, see Fisher Q
Hiller JM, see Wang BC
Hillier SC, Presson RG Jr, Godbey PS, Okada O, Wagner WW Jr. Direct measurement of canine pulmonary microvascular compliance, S108
  Presson RG Jr, Haselby KA, Rao CC. Pressure transducer performance inside a magnetic resonance imaging scanner, S109
  see Presson RG Jr
Hindman BJ, see From RP
Hines R, Rinder C, Perrino A, O'Connor R, Lippman A. A method to reduce PACU complications: monitoring lower esophageal contractility, S110
  see Rafferty T
Hirakawa M, see Yokoyama M
Ho I, see Grant GJ
Ho ST, Lin BH, Ho W, Lin CY. Effects of succinylcholine on the recovery of vecuronium-induced neuromuscular blockade, S111
Ho W, see Ho ST
Hoffman S, see Shoemaker S
Hoffman WE, Ferguson RL, Miletich DJ, Albrecht RF. Cerebral perfusion with saline improves outcome from incomplete ischemia in rats, S112
  see Cheng MA
Housmans PR
  see Baele PL
  see Carton EG
  see Cook DJ
Hovig T, see Kongsgaard UE
Howard G, see Khalil S
Howe JP, see Wright PMC
Howie MB, Duarte JA, Rypel GD, Romanelli VA, Rezael A. Pentamorphone vs. fentanyl in balanced anesthesia during general surgery, S113
  Galbraith TA, Romanelli VA, Rypel GD, Guertin MG, McSweeney TD. Titration of barbiturate cerebral protection to an isoelectric EEG prior to circulatory arrest, S114
  Romanelli VA, McSweeney TD, Vigder DM, Byrne BA. The effect of isoproterenol on myocardial ischemia using impedance as an indicator, S115
Hubbell D, see Miguel R
Hudson JC, Gennings C, Kane FR, Tyler BL, Keenan RL. Intraoperative complication rates during elective and emergency procedures, S116
Hug CC Jr, see Falinski B
Humphreys HK, Jones BR. Blood coagulation is delayed after passage through an epidural catheter, S117
Hung W-T, see Wang J-S
Hurford WE, see Szabo MD
Hurst T, see Chang P
Hwang WJ, see Erian RF
Hyatt J, see Barker SJ
Hynson J, see Sessler DI
Hynson JM, Sessler DI, Moayeri A, McGuire J. Absence of nonshivering thermogenesis in anesthetized adults, S119
  Sessler DI. Comparison of intraoperative warming devices, S118

Iacono C, see Zavisca F
Ichinohe T, see Kaneko Y
Iftikhar M, see Orr DA
Igarashi O, see Kaneko Y
Ilyes L, see Schubert A
Inada E, Aoki K, Aoki H, Kohama M, Takanashi S, Iwahashi K, Furuta S. Relationship between antithrombin III-heparin complex and activated clotting time in cardiac surgery, S120
Isetta C, Roul C, Samat C, Kotaiche M, Jourdan J. Platelet aggregation and fibrinolytic activity during cardiopulmonary by-pass, S121
Ivankovich A, see Fischer R
Ivankovich AD
  see Parnass SM
  see Sosis M
  see Spiess BD
  see Tuman KJ
Ivanov J, see Teasdale S
Iwahashi K, see Inada E
Iwasaki H, see Ohta K

Jacobs BR, O'Connor TZ. Controlled comparison of the antiemetic efficacy of thiethylperazine and droperidol outpatient surgery, S122
Jacobson L, Chabal C, Mariano A, Chaney Intrathecal fentanyl in the evaluati of persistent low back pain, S124
  Chabal C, Mariano A, Chaney E. The combination of intrathecal morphi and PCA provides excellent postoperative analgesia, S123
Jahr JS, see Haskins DA
Jain S, Shah N, Bedford R. Needle positio for paravertebral and sympathetic nerve blocks: radiologic confirmati is needed, S125
Jain U, Rao TLK, Krishnamurthy A, Walli DE, Moran JF. Intraoperative ischemia: compared to what?, S126
Jamdar S, see Matteo RS
Jantzen J-P, Hennes HJ, Klein AM, Kemps O. Porcine 'masseter spasm' is no spasm, S127
Jarnberg P-O, Priano LL. Droperidol bloc ephedrine induced increases in ren blood flow in halothane anesthetiz dogs, S128
Jebeles JA, Reilly JS, Gutierrez JF, Bradley EL Jr, Kissin I. Effect of infiltration anesthesia on posttonsillectomy pai S129
Jellish WS, see Modica PA
Jewell MR, see Kerkar P
Johnson D, see Chang P
Johnston D, see Milligan KR
Jones BR, see Humphreys HK
Jones CW, see Christie JM
Jones D, see Spiess BD
Jones KA, see Stensrud PE
Jorgensen NA, Messick JM, Nugent M, Gr J, Berquist TH, Forbes GS. Patient monitoring during MRI, S130
Jorgensen NH. Postdural puncture headache is more common with th paramedian approach, S131
Jourdan J, see Isetta C

Kafer ER, see Blau WS
Kampine JP
  see Berens RJ
  see Boban M
  see Cheng EY
  see Eskinder H
  see Flynn N
  see Laszlo A
  see Mehner RW
  see Pagel PS
  see Schedewie HK
  see Stadnicka A
  see Stowe DF
  see Supan F
  see Turner LA
  see Warltier DC
Kane FR, see Hudson JC
Kaneko Y, Ichinohe T, Igarashi O, Nakaku T, Fukunaga AF. Intravenous ATP ameliorates cardiovascular and

respiratory functions during anesthesia in surgical patients, S132
Karliczek G, see Renz D
Karp R
  see Lin CY
  see Wang J-S
Karski J, see Teasdale S
Kartha R
  see Dalisan J
  see El-Naggar M
Kaseno S, see Dozaki S
Kataria B, see Dubois M
Kearney E, see Wright PMC
Keaveny J, Clarke E, Pleuvry B, Whittaker DK. Midazolam levels in the isolated cardiopulmonary circuit, S133
Keenan RL, see Hudson JC
Keller I, see Schwender D
Kelley D, see Haskins DA
Kelley SD, Csete Prager M, Bissell DM. Interaction of tissue-type plasminogen activator with hepatic cells: a model for liver transplantation, S134
Kelliher G, see Norden J
Kelly JW, see Fukuoka RH
Kemmotsu O, Otsuka H, Ueda M, Yamamura T, Ekerle JS, Winter DC. Arterial tonometry for blood pressure monitoring in pediatric anesthesia, S135
  see Dozaki S
  see Harada K
  see Yamamura T
Kempski O, see Jantzen J-P
Kennedy D, see Walmsley PNH
Kerkar P, Jewell MR. Do intraoperative CV complications prolong hospital stay for same-day pediatric patients?, S136
Keykhah MM, see Bennett JA
Khairallah PA
  see Ebrahim Z
  see Yamanoue T
Khalil S, Howard G, Messamore A, Hanis C, Ruiz R. Alfentanil decreases the jerky movements and cough associated with intravenous methohexital, S137
Khan J, see Kovac A
Khoo P, see Zakowski M
Khyriem VR, see Kiran U
Kim S, see Meyer P
Kim S-J
  see Abdel-Latif M
  see Crystal GJ
Kimura K, see Fujita Y
Kiran U, Khyriem VR, Saxena N. Evaluation of vecuronium for tracheal intubation in paediatric cardiac patients, S138
Kirby RR, see Banner MJ
Kirkman RL, see Shafer AL
Kissin I
  see Jebeles JA
  see Vinik HR
Kitahata LM, see Spencer RF
Kittle F
  see El-Baz N
  see Faber L
Kleiman SJ, Wiesel S, Kliffer AP. Interpleural blockade produces effective analgesia in the elderly, S139
  see Kliffer AP
Klein AM, see Jantzen J-P
Klein G, see Sharpe MD
Kliffer AP, Wiesel S, Lubenskyi W, Kleiman SJ. Interpleural bupivacaine does not lead to elevated plasma levels in the elderly, S140
  see Kleiman SJ
Klochany A, see Falinski B
Knight PR, see Tait AR
Kobayashi K
  see Kondo T
  see Toriumi K
Kohama M, see Inada E
Komar WE, see Moote CA
Komura Y, see Dozaki S
Kondo T, Yasuda N, Tanifuji Y, Kobayashi K, Miyano K. Serum inorganic fluoride concentration following anesthesia with sevoflurane in anuric patients, S141
Kongsgaard UE, Geiran O, Brosstad F, Hovig T. Platelets in shed mediastinal blood used for postoperative autotransfusion, S142
  Smith-Erichsen N. Haemodynamic effects of heparin during coronary bypass surgery, S143
Kopel RF, see Durbin CG Jr
Korttila K, see Lehtinen A-M
Korver K, see Muhiudeen IA
Kosinski R, see Patel N
Kotaiche M, see Isetta C
Koufman JA, see Olympio MA
Kovac A, Bennetts P, Ohara S, LaGreca B, Khan J, Calkins J. Effect of esmolol on hemodynamics and intraocular pressure response to succinylcholine and intubation, S144
Kramer GC, see Pascual JMS
Kraynack BJ, Bates MF. IV ranitidine reduces nausea and vomiting after propofol-isoflurane anesthesia, S145
Kreiter CD, see From RP
Kress HG, Woltmann A. Is anergy soon after multiple trauma really associated with poor outcome?, S146
Krishnamurthy A, see Jain U
Kristensen J, Modig J. Ringer's acetate or dextran 70, with or without hypertonicity, in the treatment of endotoxin shock in pigs, S147
Krom RAF, see Dubbink DA
Kross R, Shah N, Shah S, Alagesan R, Rodman R. Unexpected risk factors for the development of hypotension during anesthesia, S148
Kumatta D, see Flanagan JF
Kwan W-F, Lee C, Tsai SK, Chen B-J, Cantley E. Emergence from desflurane (I-653) or isoflurane anesthesia at 0.65 MAC with 60% nitrous oxzide, S150
  see Tsai SK
Kwan WF, Chuah EC, Chen BJ, Wong SY. Epidural opioids and lidocaine given before baby delivery for cesarean section in Chinese parturients: efficacy and safety, S149
Kytta J, see Zavisca F

LaGreca B, see Kovac A
Lamer TJ, see Lee TL
Lampotang S, Nyland ME, Gravenstein N. The cost of wasted anesthetic gases, S151
Landymore RW
  see Hall RI
  see Murphy JT
Lane B
  see Apfelbaum JL
  see Lichtor JL
Lang S, see Chang P
Langner R, see Battito MF
Lapeyre G, see Dubois M
Larson AA, see Baker AJ
Larson C, see Cheng K
Laszlo A, Atlee JL, Polic S, Kampine JP, Bosnjak ZJ. Inhalation anesthetics and triggered sustained rhythmic activity in Purkinje fibers from infarcted canine hearts, S152
  Bosnjak ZJ, Polic S, Kampine JP, Turner LA, Atlee JL. Effects of inhalation anesthetics on normal and abnormal automaticity of Purkinje fibers, S153
  see Turner LA
Latson T, see Gulden RH
Lawson S, see Sandler AN
Layon AJ, Burke BE, Gallagher TJ. Age and outcome after craniotomy, S154
Le N, see Barker SJ
Lea D, see Dubois M
Lee B, see Wang J-S
Lee C
  see Gyermek L
  see Kwan W-F
  see Tsai SK
Lee DH, see Murkin JM
Lee EW, Pace NL, Peters JL. Do histamine H2 blockers work under anesthesia? The effects of ranitidine given intraoperatively on gastric pH and volume, S155
Lee TL, Lamer TJ. Outpatient intrathecal morphine for chronic pain patients, S156
  Lennon RL. Emergent reintubation in the postanesthesia recovery room, S157
Lehtinen A-M, Aho M, Erkola O, Korttila K. Dexmedetomidine reduces cortisol and β-endorphin responses to intubation and laparoscopy, S158
  see Aho M

Leicht CH, Evans DE, Durkan WJ, Noltner S. Sufentanil vs fentanyl intrathecally for labor analgesia, S159
Lennon R
  see Bires J
  see McGregor D
Lennon RL
  see Ereth MH
  see Lee TL
  see Stensrud PE
Leon J, Bissonnette B, Lerman J. Does cerebrovascular hysteresis exist under isoflurane anesthesia in children?, S160
  Bissonnette B, Lerman J. Does halothane affect the cerebrovascular response to carbon dioxide in anesthetized children?, S161
Leon M, see Christie JM
Leone BJ, see Spahn DR
Lerman J
  see Leon J
  see Sloan M
Lessin J
  see Rosenblum F
  see Schieren H
Lessin JB, Azad SS, Rosenblum F, Bartkowski RR, Marr A. Does antiemetic prophylaxis with ondansetron prolong recovery time?, S162
Levin D, see Erian RF
Lewis BK, see Fleming NW
Li D, see Wang BC
Liao KT, see Tsai SK
Lichtor JL, Apfelbaum JL, Lane B, Coalson D, Uitvlugt A, Rupani G, Schreider B, Glosten B, Roizen MF, Finn R. Long-term recovery: desflurane vs propofol, S163
  see Apfelbaum JL
  see Boucaud C
  see Dohrn CS
Licina MG, Starr NJ, Estafanous FG, Smith CE, Blum JM, Bednarski M. Transdermal nitroglycerin does not reduce the incidence of prebypass ischemia in patients undergoing coronary artery bypass grafting, S164
Lieponis J, see Brull SJ
Lin BH, see Ho ST
Lin CY, Theo C, Finn R, Aronson S, Karp R, Yang M-W. Another application of transesophageal echocardiography-aortic annulus measurement, S165
  see Ho ST
  see Wang J-S
Lingaraju N, see Bennett JA
Lippman A, see Hines R
Lippmann M, see Tsai SK
Lipton JM, see Gulden RH
Little JR, see Schubert A
Liu L, see Welborn L
Lok P, see Badner NH
Looker D, see Shoemaker S
Loop FD, see Higgins T
Lubenskyi W, see Kliffer AP
Lynd H, see Walmsley PNH

MacDonald LE, Franklin C, Wiseman E. Using a head covering of T-727 thermal fabric to conserve core body temperature during anesthesia, S166
Machado AF, see Cohn ML
Madler C, see Schwender D
Mahla ME, Pashayan AG, Grundy BL, Mixson S, Richards R, Day AL. Mental recovery parameters after prolonged anesthesia with propofol, S167
  see Pashayan AG
Mahoney LT, see Murray DJ
Mangar D, de Sousa H, Camporesi E. Electrocardiographic changes associated with the prone position: a pilot study, S168
Manninen PH, Gignac EA, Gelb AW. Anesthesia for interventional neuroradiology, S169
  see Gignac MA
Mantia AM, Robinson JN, Myers BB, Stullken EH Jr. Can steroids decrease CPK-MB levels in CABG patients?, S170
March R, see Tuman KJ
Mariano A, see Jacobson L
Marijic J, see Buljubasic N
Maritime Heart Centre, see Hall RI
Marr A
  see Lessin JB
  see Rosenblum F
Martin E
  see Spies C
  see Zuane U
Martin RL, Stevens WC. Inspiratory effort is a sensitive guide to anesthetic depth, S171
  see Stevens WC
Mason WR, see Crystal GJ
Mathew J, see Rafferty T
Mathew M, see El-Naggar M
Mathews D, see Cohen S
Mati N, see Chung F
Matsumoto M, see Ohta K
Matteo RS, Schwartz AE, Ornstein E, Jamdar S, Diaz J, Rodrigues H, Weinberger M. Pharmacokinetics and pharmacodynamics of pipecuronium in elderly surgical patients, S172
Maurer PH, see Maurer PM
Maurer PM, Grun JL, Torjman M, Schieren H, Maurer PH, Seltzer JL. Effects of volatile anesthetics on antigen-specific T-cell immune responses, S173
Mayers I, see Chang P
Maze M
  see Correa-Sales C
  see Guo T-Z
McCarthy R, see Fischer R
McCarthy RJ
  see Parnass SM
  see Spiess BD
  see Tuman KJ
McComiskey G, see Fisher Q
McDonnell FJ, see Walmsley PNH
McElrath T, see Bennett JA
McGill W, see Welborn L
McGill WA, see Mostello LA
McGregor D, Bires J, Lennon R. Intubatior with low dose atracurium and vecuronium in infants and childrer S174
  see Bires J
McGuire J, see Hynson JM
McGuire JP, Sessler DI. Perioperative thermal insulation, S175
McKinney MS, Fee JPH. Cardiovascular effects of halothane in young and elderly adults, S176
  Fee JPH. Cardiovascular effects of isoflurane in young and elderly adults, S177
  Fee JPH. Inhalation induction with isoflurane in adults, S178
McManus M, see Pilato MA
McMillan DW, Gold MI, deLisser EA, Palermo NN. Desflurane: how does compare to isoflurane in elderly patients?, S179
McRae RL, see Spahn DR
McSweeney TD, see Howie MB
Meert T, Mesens J, Verheyen P, Noorduin Vercauteren M. Hydroxypropyl-B-cyclodextrin can potentiate the analgesic properties of spinal sufentanil in rats, S180
  see Vercauteren M
Mehner RW, Buljubasic N, Boban M, Stow DF, Kampine JP, Bosnjak ZJ. Combined effects of verapamil and halothane on pressure recovery aft hypoperfusion in guinea pig hearts S181
Mehta MP, Sum-Ping JST, Symreng T. Assessment of vital capacity breathing during denitrogenation, S182
  see Symreng T
Mesens J, see Meert T
Messamore A, see Khalil S
Messick JM, see Jorgensen NA
Meyer P, Thisted R, Roizen MF, Gronert Murray WJ, Grogono AW, Duke P, Kim S, Apfelbaum J, Rupani G, Texidor P, White PF, Poler SM, Coalson D, Youngberg JA, Dionne Stocking C. Improving perioperativ laboratory test selection, S183
Mick S, see Sebel PS
Mick SA, see Fletcher JE
Mickler TA, see Fisher SM
Miguel R, Hubbell D. Postthoracotomy pai cryoanalgesia versus intrapleural analgesia, S184

Mike N, see Fujiwara Y
Miletich DJ
  see Cheng MA
  see Hoffman WE
Miller CG, see Whitehead E
Miller RD
  see Segredo V
  see Szenohradszky J
Milligan KR, Cramp P, Schatz L, Johnston D, Carp H. The effect of positioning and obesity on epidural analgesic spread, S185
Mills AK, see Roa NL
Mitterschiffthaler G. Lidocain -HCl or -CO$_2$ for brachial plexus block in patients with chronic renal failure?, S186
Mixson S, see Mahla ME
Miyano K, see Kondo T
Moayeri A, see Hynson JM
Modica PA, Jellish WS, Tempelhoff R. EEG-quantified anesthesia: influence on myocardial infarction rate during carotid endarterectomy, S187
Modig J, see Kristensen J
Moffitt EA
  see Hall RI
  see Murphy JT
Mohindra P, see Shenaq SA
Mok MS, see Tsai SK
Molotiu N, see Dobkowski WB
Monk TG, Smith I, White PF. Propofol infusion: sedative, amnestic, and anxiolytic effects, S188
Moody C, see Schieren H
Moore J, see Orr DA
Moote CA, Dobkowski WB, Komar WE. Complications of postoperative intravenous and epidural narcotic analgesia, S189
  Varkey GP, Komar WE. Similar incidence of post-dural puncture headache after conventional vs continuous spinal anesthesia, S190
Moran JF, see Jain U
Morgan PG, see Sedensky MM
Morimoto Y, see Dozaki S
Mortiz H, see Podraza A
Mostello LA, Casey WF, McGill WA. Does the use of a surgical tourniquet induce fever in infants?, S191
Mostrom JR, see Rung GW
Motis V, see Weinger MB
Moyers JR, see From RP
Muhiudeen IA, Roberson DA, Silverman NH, Cahalan MK, Korver K, Haas GS, Turley K. Transesophageal echocardiography of congenital heart defects in infants and children, S192
Mulroy JJ, Davis PJ, Cook R. Hemodynamic responses and recovery from alfentanil in children, S193
Muratori F, see Capogna G
Murdoch C, see Sharpe MD
Murkin JM, Lee DH. Transcranial Doppler verification of pulsatile cerebral blood flow during cardiopulmonary bypass, S194
  see Badner NH
  see Dobkowski WB
  see Sharpe MD
Murphy JT, Moffitt EA, Hall RT, Landymore RW, Sullivan JAP, Wood JR. Myocardial oxygenation and ischemia in hypertensive patients undergoing coronary revascularization, S195
  see Hall RI
Murphy M, see Brull SJ
Murphy MR
  see Fletcher JE
  see Sebel PS
Murray D, see From RP
Murray DJ, Forbes RB, Mahoney LT. Comparative cardiovascular depression of halothane and isoflurane in neonates, S196
Murray MJ, see Nuttall GA
Murray WJ, see Meyer P
Muzi M, see Berens RJ
Myers BB, see Mantia AM

Nagano O, see Foldes FF
Nakakuki T, see Kaneko Y
Nakatsuka M. Comparison of hemodynamic response to cardioversion with methohexital and etomidate, S197
  Campbell R. Hemodynamic and respiratory effects of transtracheal high frequency jet ventilation during difficult intubation, S198
  see Risenmay AK
Namiki A, see Ohta K
Naoe T, see Fujiwara Y
Negus S, see Weinger MB
Neuenfeldt T, see Freund PR
Newman SP, see Stump DA
Nguyen N, see Gyermek L
Nichols WL, see Nuttall GA
Noltner S, see Leicht CH
Noorduin H, see Meert T
Norden J, Hannallah R, Getson P, O'Donnell R, Kelliher G, Walker N. Reliability of an objective pain scale in children, S199
Norman P, see Sandler AN
Norman PH, Daley MD. Sandler AN. Preoperative respiratory monitoring in thoracic patients, S200
Nugent M, see Jorgensen NA
Nuttall GA, Oliver W, Beynen FM, Dull JJ, Murray MJ, Nichols WL. Intraoperative measurement of APTT and PT by portable laser photometer, S201
Nyland ME, see Lampotang S

O'Brien HV, Splinter WM. Butorphanol: a narcotic for day-care pediatric surgery, S202
O'Connor T
  see Hines R
  see Rafferty T
O'Connor TZ
  see Jacobs BR
  see Silverman DG
  see Spencer RF
  see Yang JT
O'Donnell R, see Norden J
Offord KP, see Warner MA
Ogawa T, see Shibutani K
O'Hara J, see Ebrahim Z
Ohara S, Goto K, Torline RL, Goto H, Arakawa K. Monitoring of left ventricular transmural pressure in acute cardiac tamponade, S203
  see Kovac A
Ohta K, Takahashi I, Iwasaki H, Matsumoto M, Namiki A. Dose-response relationship of oral clonidine in tetracycline spinal anesthesia, S204
Ohta Y
  see Foldes FF
  see Vizi ES
Okada O
  see Hillier SC
  see Presson RG Jr
Okamura A
  see Dozaki S
  see Harada K
Oliker R, see Guo-T-Z
Oliver W, see Nuttall GA
Olympio MA, Haisty WK, Pahlm O, Koufman JA, Weeks DB. Detection of myocardial ischemia during suspension microlaryngeal surgery, S205
Ong D
  see Cheng DCH
  see Chung F
Ornstein E, see Matteo RS
Orr DA, Iftikhar M, Beattie RB, Bill KM, Thompson WB, Moore J. Thiopentone and propofol in obstetrics: effects on the fetoplacental circulation, S206
Orsina M, see Durbin CG Jr
Orsina MA, see Durbin CG Jr
Osborne TN, see Schell RM
O'Sullivan G, see Whitehead E
Otsuka H, see Kemmotsu O

Pace NL, see Lee EW
Pagel PS, Schmelling WT, Kampine JP, Warltier DC. Effects of desflurane and isoflurane on myocardial contractility in chronically instrumented dogs, S207
Pahlm O, see Olympio MA
Paige D, see Silverman DG
Palermo NN, see McMillan DW
Paranandi L, see Schubert A
Parnass SM, Corey ER, McCarthy RJ, Ivankovich AD. Droperidol and metoclopramide do not provide

effective antiemetic prophylaxis in outpatient knee arthroscopies, S208
Pasch T, see Atanassoff PG
Pascual JMS, Watson JC, Runyon DE, Wade CE, Kramer GC. Management of intraoperative hypovolemia in swine using 7.5% hypertonic sodium chloride in 6% dextran, S209
Pashayan AG, Grundy BL, Mahla ME, Shah BD. Comparison of sufentanil, fentanyl, and isoflurane for neuroanesthesia, S210
  see Mahla ME
Pasricha SK, see Subhedar DV
Patel D, see Fahmy NR
Patel N, Strogen C, Kosinski R, Antiporda C, Yuvorek G, Baker T. The rapid recovery of respiratory function after laparoscopic cholecystectomy, S211
Patil AR, see Shafer AL
Pauli HMF, see Zaune U
Paull JP, see Zelcer J
Paulsen AW. Low pass filtering of arterial pressure signals can improve accuracy: a study based on a canine model, S212
Pearson KS, Scamman FL. Quality assurance monitoring and evaluation in a Veterans Affairs Hospital: 30 months of data, S213
  see From RP
Pedigo NW, see Walmsley PNH
Peller DP, see Stowe DF
Perrino A, see Hines R
Peter K, see Stein C
Peters JL, see Lee EW
Peterson N, see Dwyer R
Piccione W, see Spiess BD
Pilato MA, Everts E, Yemen T, McManus M, Farrugia R, Gillis J, Greenblatt D. Premedication in pediatric outpatient surgery: comparison of oral midazolam to rectal methohexital, S214
Plate JF, see Fisher SM
Pleuvry B, see Keaveny J
Podraza A, Salem MR, Harris TL, Moritz H. Effects of bellows leaks on anesthesia ventilator function, S215
Poler M, see Van Hemelrijck J
Poler SM, see Meyer P
Polic S, see Laszlo A
Polk A, see Boucaud C
Polk S, see Boucaud C
Pool JM, see Sidi A
Poppel E, see Schwender D
Posner K, see Freund PR
Powell P, see Chung F
Preble L, see Rosenblatt W
Preble LM, see Silverman DG
Presson RG Jr, Hillier SC, Okada O, Wagner WW Jr, Hakim TS. Measurement of pulmonary capillary pressure from the arterial occlusion pressure curve in dogs, S216
  see Hillier SC
Priano LL, see Jarnberg P-O
Prough DS
  see Stump DA
  see Williamson WK

Quinn T, see Sun X

Radford P, see Ravalia A
Rafferty T, Durkin M. Cardioplegic contrast echocardiography in patients with aortic regurgitation, S217
  Durkin M, Hines R, Elefteriades J, O'Connor T. Effects of pericardectomy on right ventricular dynamics, S218
  Durkin M, Mathew J, O'Connor T. Estimation of tricuspid regurgitation: color-flow Doppler versus saline-contrast echocardiography, S219
Ramadyhani U, see Haskins DA
Ramanathan S
  see Grant GJ
  see Rosenberg AD
  see Waters JJ
  see Zakowski M
Rao CC, see Hillier SC
Rao TLK, see Jain U
Ravalia A, Fawcett W, Radford P. The brain laryngeal mask airway in paediatric anesthesia, S220
Reilly JS, see Jebeles JA
Reinsel R, see Gatell JA
Renz D, Karliczek G. Influence of anesthetic technique on cerebral blood flow velocity autoregulation during low flow cardiopulmonary bypass, S221
Rettke SR, see Dubbink DA
Reynolds B, see Chang P
Rezael A, see Howie MB
Rhoton FM, see Schubert A
Richards R, see Mahla ME
Richlin D, see Handlin DS
Riegler FX. Brachial plexus neurostimulation: motor response patterns at three sites, S222
Riemondy S, see Rung GW
Rinder C, see Hines R
Rinder CS, Rinder HM, Smith BR. CPB-associated platelet receptor loss continues into the post-bypass period, S223
Rinder HM, see Rinder CS
Risenmay AK, Nakatsuka M. Comparison of the effect of a small bolus dose of esmolol and labetalol on the hemodynamic response to ECT therapy, S224
Roa NL, Exler J, Young LV, Mills AK. Use of high-dose mepivacaine for axillary brachial plexus block, S225
Roberson DA, see Muhiudeen IA
Roberts JT, see Shorten GD
Robinson JN, see Mantia AM
Rodes WD II, Banner MJ, Gravenstein N. Variations in imposed work of breathing with heat and moisture exchangers, S226
Rodkey WG, see Snodgrass GW
Rodman R, see Kross R
Rodrigues H, see Matteo RS
Rogers AT, see Williamson WK
Roizen MF
  see Apfelbaum JL
  see Lichtor JL
  see Meyer P
Romanelli VA, see Howie MB
Rooney ME, Code WE. Can the NSAID naproxen reduce post-operative pai in laparoscopic tubal ligation?, S227
Rosenberg AD, Bernstein D, Skovron ML, Ramanathan S, Turndorf H. Are anesthesiologists practicing proper infection control precautions?, S228
Rosenberg P
  see Heavner J
  see Zavisca F
Rosenblatt W, Saberski L, Sinatra R, Silverman D, Cioffi A, Preble L. Metoclopramide: an analgesic adjunct to PCA?, S229
Rosenblum F, Azad SS, Bartkowski R, Seltzer J, Lessin J, Marr A. Ondansetron: a new, effective anti-emetic prevents postoperative nausea and vomiting, S230
  see Lessin JB
Roul C, see Isetta C
Roy RC, see Williamson WK
Ruiz R., see Khalil S
Rung GW, Clark SK, Mostrom JR, Riemondy S. Evaluation of a 32 gauge catheter for continuous spina anesthesia during lithotripsy, S231
Runyon DE, see Pascual JMS
Rupani G
  see Apfelbaum JL
  see Boucaud C
  see Lichtor JL
  see Meyer P
Rush W, see Pool JM
Ryan K, see Fletcher JE
Rypel GD, see Howie MB

Saberski L, see Rosenblatt W
Saied MMA, Sonbul ZM, El-Kenawy M, Atallah MM. Spinal and interpleura bupivacaine for percutaneous nephrolithotomy, S232
Salem MR
  see Abdel-Latif M
  see Crystal GJ
  see Podraza A
Salter O, see Cohen E
Samat C, see Isetta C
Samson B, see Sandler AN
Sandler AN, Baxter AD, Norman P, Samso B, Lawson S, Hull K. A double-blin placebo-controlled trial of transdermal fentanyl, for post-

hysterectomy analgesia, S233
  see Norman PH
Sarner J, see Welborn L
Sarner JB, see Woelfel SK
Sato K, see Yamamura T
Saxena N, see Kiram U
Scamman FL, see Pearson KS
Scavone JA, see Snodgrass GW
Schatz L, see Milligan KR
Schawalder J, see Atanassoff PG
Schedewie HK, Boban N, Kampine JP, Bosnjak ZJ. Calcium dependent inhibition of synaptic ganglionic transmission by isoflurane in the dog, S234
Schell RM, Cole DJ, Osborne TN. Pentastarch decreases blood-brain barrier permeability following temporary cerebral ischemia in rats, S235
Scheller MS, see Baker AJ
Schieren H, Heropoulos M, Seltzer JL, Bartkowski RR, Torjman MC, Lessin J, Moody C, Goldberg ME. Intraoperative catecholamine: renin and hemodynamic responses following prophylactic administration of intravenous enalaprilat, S236
  see Grunwald Z
  see Maurer PM
Schleinzer W, see Singbartl G
Schmelling WT
  see Pagel PS
  see Warltier DC
Schreider B
  see Apfelbaum JL
  see Lichtor JL
Schroeder T, see Heidelmeyer CF
Schubert A, Bloomfield E, Little JR, Ebrahim ZY, Grimes-Rice M, Paranandi L. Do location and size of brain tumor affect emergence from anesthesia?, S237
  Rhoton FM, Sords S. Mock oral examinations results are unrelated to daily faculty evaluations, S238
  Walsh M, Ilyes L. Do temperature and dilution affect the sealability of pinhole endotracheal cuff leaks?, S239
Schulman SR. The effect of gastric suction on postoperative nausea and vomiting in children, S240
Schwartz AE, see Matteo RS
Schwender D, Madler C, Keller I, Poppel E. Propofol suppresses neuronal oscillations in auditory evoked potentials, S241
Sebastiani M, see Capogna G
Sebel PS, Murphy MR, Fletcher J, Mick S. Ocfentanyl in balanced anesthesia: comparison with fentanyl, S242
  see Falinski B
  see Fletcher JE
Sedensky MM, Morgan PG. Characterization of a mutation affecting sensitivity to volatile anesthetics in *C. elegans*, S243
Segredo V, Caldwell JE, Sharma ML, Gruenke LD, Miller RD. Long term administration alters the pharmacokinetics of vecuronium, S244
  see Szenohradszky J
Seltzer J, see Rosenblum F
Seltzer JL
  see Bartkowski RR
  see Maurer PM
  see Schieren H
Sessler DI, Hynson J. Electromyographic analysis of tremor patterns during epidural anesthesia, S245
  see Ereth MH
  see Hynson JM
  see McGuire JP
  see Sladen R
Seyone C, see Chung F
Shafer AL, Patil AR, Dewan JA, Kirkman RL. Oral prophylaxis of acid aspiration syndrome: a comparison of famotidine and ranitidine, S246
Shah BD, see Pashayan AG
Shah N
  see Jain S
  see Kross R
Shah P, see Shibutani K
Shah S, see Kross R
Shapira Y, Cotev S, Shohami E. Methylprednisolone does not affect brain edema following head trauma in rats, S247
Shapiro HM, see Baker AJ
Sharma A, see Sharpe MD
Sharma M, see Szenohradszky J
Sharma ML, see Segredo V
Sharpe MD, Murkin JM, Dobkowski WB, Murdoch C, Sharma A, Klein G, Guiraudon G, Yee R. Sufentanil anaesthesia has no effect on conduction of normal and accessory pathways in patients with Wolff-Parkinson-White syndrome, S248
  see Dobkowski WB
Shenaq SA, Mohindra P, Svenssen L, Crawford ES. Anesthesia for thoracoabdominal aortic aneurysm: the impact of cerebrospinal fluid drainage, S249
Shibutani K, Ogawa T, Babu S, Shah P. Mechanisms of blood pressure changes following infra-renal aortic cross-clamping, S250
  Whelan G, Zung N, Ferlazzo P. End-tidal CO_2: a clinical noninvasive cardiac output monitor, S251
  see Subhedar DV
Shimada Y, see Fujiwara Y
Shoemaker S, Hoffman S, Stetler G, Looker D. Modifications engineered into recombinant hemoglobin decrease toxicity and improve efficacy in rats, S252
Shohami E, see Shapira Y
Sholte FG, see Swayze CR
Shono S, see Tanaka K
Shorten GD, Ali HH, Roberts JT. Assessment of patient position for fiberoptic intubation using videolaryngoscopy, S253
Sidi A, Pool JM, Rush W. Stellate ganglion ablation, hemodynamic and metabolic impairment, and acute coronary hypoperfusion in dogs, S254
Siler JN, Fisher SM, Boon P. Propofol (P) for total intravenous anesthesia without nitrous oxide or narcotic infusion, S255
Silverman D, see Rosenblatt W
Silverman DG, Preble LM, Paige D, O'Connor TZ, Brull SJ. Basal intubation as supplement to PCA in orthopedic patients, S256
  see Brull SJ
  see Spencer RF
  see Yang JT
Silverman NH, see Muhiudeen IA
Simon EJ, see Wang BC
Sinatra R, see Rosenblatt W
Singbartl G, Schleinzer W. The concept of autologous transfusion - a prospective one year's study in over 4,000 orthopaedic-surgical patients, S257
Sittipong R, see Dubbink DA
Skerman JH, see Swayze CR
Skovron ML, see Rosenberg AD
Sladen R, Sessler DI. Elevated thermoregulatory threshold for sweating during rewarming from cardiopulmonary bypass, S258
Sloan M, Lerman J, Bissonnette B. Comparison of the potency of vecuronium and atracurium in children using the EMG, S259
Sloan TB, Hickey R. Alterations in ventilation does not alter the onset of cortical magnetic motor evoked potentials, S261
  Mild hypothermia alters cortical magnetic motor evoked potentials, S260
Slucky AV, see Befacqua BK
Smith BR, see Rinder CS
Smith CA, see Fletcher JE
Smith CE, see Licina MG
Smith I
  see Monk TG
  see Van Hemelrijck J
Smith LR, see Spahn DR
Smith W, see Durbin CG Jr
Smith-Erichsen N, see Kongsgaard UE
Sneyd JR, Berry A. Glycopyrrolate does not attenuate the haemodynamic response to propofol, S262
Snodgrass GW, Burgess FW, Brooks DE, Wade CE, Scavone JA, Rodkey WG.

Influence of combined epidural/general anesthesia on the hemodynamic response to moderate hemorrhage in a swine model, S263
Sonbul ZM, see Saied MMA
Sords S, see Schubert A
Soriano S, Benthuysen J, Fung D. Vasopressin is released with catecholamines during electroconvulsive therapy, S264
Sosis M, Braverman B, Ivankovich AD. An evaluation of special tracheal tubes with the KTP laser, S267
  Evaluation of a new laser resistant anesthesia circuit protector, drape, and patient eye shield, S265
  Saline-soaked pledgets prevent CO_2 laser-induced tracheal cuff ignition, S266
Spahn DR, Smith LR, McRae RL, Leone BJ. Halothane dose response curves pre versus post cardio-pulmonary bypass in dogs, S268
Spencer RF, Silverman DG, O'Connor TZ, Kitahata LM. Does sphenopalatine block with intranasal lidocaine reduce ischemic tourniquet pain?, S269
Spevak C, see Tetzlaff JE
Spies C, Zaune U, Boeden G, Martin E. Different anesthetic regimens in pulmonary surgery, S270
  see Zaune U
Spiess BD, Jones D, McCarthy RJ, Piccione W, Corey E, Ivankovich AD. Desflurane vs isoflurane: a comparison of hemodynamics in patients undergoing coronary artery bypass, S271
Splinter WM. The effect of fentanyl on thiopental requirements in children, S272
  Torsher LC. Measurement of end-tidal PCO_2 in infants: effects of low fresh gas flows and volume-cycled ventilators, S273
  see O'Brien HV
Spurrier E, see Fisher Q
Stacey BR, see Brody MC
Stadnicka A, Flynn N, Bosnjak ZJ, Kampine JP. Effects of enflurane and isoflurane on contractile activity of isolated rabbit mesenteric veins, S274
Stapelfeldt WH, Szurszewski JH. Substance P afferents mediate cellular and systemic hemodynamic effects of propofol in guinea pigs, S275
Starr NJ, see Licina MG
Stein C, Hassan AHS, Gramsch C, Peter K, Herz A. Peripheral opioid receptors mediating antinociception in inflamed tissue of the exogenous and endogenous ligands, S276
Stein CS, Stump DA, Hager RA. Microemboli detection in the carotid artery during cardiac surgery, S277
Stensrud PE, Jones KA, Anderson EP, Lennon RL. Assessment of neuromuscular function by 50 Hz tetany: a comparison with train-of-four ratio, S278
  see Ereth MH
Stetler G, see Shoemaker S
Stevens JL, see Watcha MF
Stevens WC, Martin RL. Inspiratory effort (IE) as a sign of anesthetic depth during isoflurane anesthesia, S279
  see Martin RL
Stocking C, see Meyer P
Stowe DF, Bosnjak ZJ, Kampine JP. Comparison of N_2O with enflurane or isoflurane on contractility and O_2 utilization in guinea pig hearts, S280
  Peller DP, Bosnjak ZJ, Kampine JP. Cardiac effects of etomidate, ketamine, midazolam, propofol and thiopental on O_2 supply and demand in guinea pig hearts, S281
  see Boban M
  see Buljubasic N
  see Mehner RW
Strauss WH, see Szabo MD
Strogen C, see Patel N
Stullken EH Jr, see Mantia AM
Stump DA, Newman SP, Troost BT, Prough DS, Furberg C. Neuropsychological deficits after cardiac surgery, S282
  see Stein CS
Subhedar DV, Pasricha SK, Shibutani K. Does pre-curarization affect post-operative myalgia in cesarean section?, S283
Sullivan JAP, see Murphy JT
Sum-Ping JST
  see Mehta MP
  see Symreng T
Sun X, Quinn T, Weissman C. Patterns of sedation and analgesia in the postoperative ICU patient: a survey, S284
Sunder N, see Fahmy NR
Sung YF, Tillette T. Placebo, ephedrine and antiemetics in postoperative nausea and vomiting in ambulatory surgery patient, S285
Supan F, Buljubasic N, Eskinder H, Kampine JP, Bosnjak ZJ. Effects of halothane, isoflurane and K+ current on canine cardiac Purkinje cells, S286
  see Eskinder H
Svenssen L, see Shenaq SA
Swayze CR, Sholte FG, Walker EB, Skerman JH. Efficacy of intrathecal meperidine for labor analgesia, S287
Symreng T, Mehta MP, Sum-Ping JST, Wade EF. Preoxygenation time - influence of anthropometric and pulmonary variables, S288
  see Mehta MP
Szabo MD, Crosby G, Hurford WE, Strauss WH. Assessment of myocardial perfusion in patients with subarachnoid hemorrhage and an abnormal ECG, S289
Szenohradszky J, Segredo V, Caldwell JE, Sharma M, Gruenke LD, Miller RD. Pharmacokinetics, onset and duration of action of ORG 9426 in humans: normal vs. absent renal function, S290
Szurszewski WH, see Stapelfeldt WH

Tait AR, Knight PR. Anesthesia and upper respiratory infections: the effect of tracheal intubation, S291
Takahashi I, see Ohta K
Takanashi S, see Inada E
Takaori M, see Fujita Y
Tanaka K, Shono S, Watanabe R, Dan K. Epidural anesthesia and analgesia i safe for patients with asthma - a survey of 383 patients, S292
Tanifuji Y
  see Kondo T
  see Toriumi K
Taylor E, White PF. Use of midazolam in combination with propofol for sedation during MAC, S293
Teasdale S, Boylan J, Karski J, Ivanov J, Young P, Weisel R. Diltiazem vs nitroprusside: detection of post-CABG ischemia using pressure-volume loops, S294
Tempelhoff R, see Modica PA
Tetzlaff J, see Ebrahim Z
Tetzlaff JE, Spevak C, Yoon H, Brems J. Patient acceptance of interscalene block, S295
Texidor M, see Haskins DA
Texidor P, see Meyer P
Theo C, see Lin CY
Thisted R, see Meyer P
Thompson WB, see Orr DA
Thrush DN. Automated anesthesia record are they better?, S296
Tillette T, see Sung YF
Tinker JH, see From RP
Tinklenberg J, see Guo T-Z
Tolksdorf W, Eick C, Amberger M. Premedication in pre-school childre with oral, rectal and nasal midazolam, S297
Toriumi K, Tanifuji Y, Yasuda N, Kobayash K. Effect of prolonged anesthesia with sevoflurane vs isoflurane on serum fluoride in surgical patients, S298
Torjman M
  see Grunwald Z
  see Maurer PM
Torjman MC, see Schieren H
Torline RL, see Ohara S
Torsher LC, see Splinter WM
Triplett B, see Walmsley PNH
Troost BT, see Stump DA
Tsai SK, Lee C, Kwan W-F, Chen B-J, Cantle

E. Cognitive recovery from 0.65 MAC desflurane or isoflurane anesthesia with 60% nitrous oxide, S299
  Lippmann M, Liao KT, Mok MS. Analgesic efficacy of sacral epidural morphine vs buprenorphine in children, S300
  see Kwan W-F
Tudoric N, Coon RL, Bosnjak ZJ. Halothane and isoflurane attenuate leukotriene-D4 induced constriction of the guinea pig trachea, S301
Tuman KJ, McCarthy RJ, March R, Ivankovich AD. Epidural anesthesia/analgesia improves outcome after major vascular surgery: a hypothesis reconfirmed, S302
Turley K, see Mihiudeen IA
Turndorf H
  see Grant GJ
  see Rosenberg AD
  see Wang BC
  see Zakowski M
Turner J, see Yang JT
Turner LA, Laszlo A, Kampine JP, Bosnjak ZJ. Dromotropic effects of norepinephrine on canine Purkinje fibers exposed to isoflurane and halothane, S303
  see Eskinder H
  see Laszlo A
Tyler BL, see Hudson JC

Ueda M, see Kemmotsu O
Ueda W, see Yokoyama M
Uitvlugt A
  see Apfelbaum JL
  see Lichtor JL

Van der Linden P, Wathieu M, Gilbart E, Engelman E, Vincent JL. Intentional hemodilution in anesthetized patients reduces O_2 delivery, S304
van der Starre PJA. Ketanserin in the treatment of postoperative hypertension: the Dutch Multicenter Trial, S305
Van Duys J, see Fletcher JE
Van Hemelrijck J, Smith I, Poler M, White PF. Comparative effects of esmolol and alfentanil during propofol anesthesia, S306
Varkey GP, see Moote CA
Veit S, see Heidelmeyer CF
Vercauteren M, Meert T, Adriaensen H. Epidural sufentanil: effect of bupivacaine addition on pain relief characteristics in rats, S307
  see Meert T
Verheyen P, see Meert T
Vessey JA, see Bogetz MS
Vincent JL, see Van der Linden P
Vinik HR, Bradley EL Jr, Kissin I. Alfentanil does not potentiate hypnotic effects of propofol, S308
Vizi ES, Ohta Y, Foldes FF. Adenosine inhibits acetylcholine release from the mouse neuromuscular junction through adenosine receptors, S309
  see Foldes FF
Vogelsang J, Hayes SR. The differential effects of butorphanol, meperidine and morphine treatment of postanesthesia shaking, S310
Vyder DM, see Howie MB

Wade CE
  see Pascual JMS
  see Snodgrass GW
Wade EF, see Symreng T
Wagner WW Jr
  see Hillier SC
  see Presson RG Jr
Walker EB, see Swayze CR
Walker N, see Norden J
Wallis DE, see Jain U
Walmsley PNH, Kennedy D, Lynd H, Triplett B, McDonnell FJ, Colclough G, Witt WO, Pedigo NW. Advantages in postoperative recovery of light general/epidural anesthesia, S311
Walsh M, see Schubert A
Wang BC, Li D, Hiller JM, Simon EJ, Budzilovich G, Turndorf H. Epidural EDTA induces tetanic contractions in rats, S312
Wang J-S, Hung W-T, Lin CY, Lee B, Karp R. The value of thromboelastogram in assessment of postoperative hemorrhage, S313
Warltier DC, Schmelling WT, Kampine JP, Hartman JC. Multivessel coronary artery disease with enhanced collateralization in dogs: isoflurane vs. adenosine, S314
  see Pagel PS
Warner MA, Warner ME, Weber JG, Offord KP. Postoperative pulmonary complications: more common with enflurane than isoflurane?, S315
Warner ME, see Warner MA
Warren W
  see El-Baz N
  see Faber L
Watanabe R, see Tanaka K
Watcha MF, White PF, Chu FC, Stevens JL. Effect of propofol on postoperative vomiting after strabismus surgery, S316
Waters JJ, Ramanathan S. A re-evaluation of the pentothal test to detect CSF in the epidural catheter aspirate, S317
Waters V, see Yamanoue T
Wathieu M, see Van der Linden P
Watson JC, see Pascual JMS
Waxler B, Zhang X, Wezeman F. The effects of anesthetics on proteinase inhibitors in C57BL/6 mouse, S318
Weber JG, see Warner MA
Weeks DB, see Olympio MA
Weinberger M, see Matteo RS
Weinger MB, Motis V, Negus S. Alfentanil-induced muscle rigidity is antagonized by central administration of kappa agonists in the rat, S319
Weisel R, see Teasdale S
Weissman C
  see Cohen S
  see Sun X
Welborn L, Zwass M, Coté C, Davis P, Dinner M, Hannallah R, McGill W, Fisher D, Liu L, Cook R, Sarner J. Comparison of desflurane and halothane anesthesia in pediatric ambulatory patients, S320
Weldon BC, White PF. Oral midazolam-meperidine-atropine premedication in pediatric outpatients, S321
Weller RS, Conard P, Gross JB. Flumazenil reverses midazolam-induced ventilatory depression in man, S322
Wezeman F, see Waxler B
Wheeler DS, see Brody MC
Whelan G, see Shibutani K
White DA, see Fleming NW
White PF
  see Baron MJ
  see Chandler LH
  see Ghouri AF
  see Meyer P
  see Monk TG
  see Taylor E
  see Van Hemelrijck J
  see Watcha MF
  see Weldon BC
  see Zelcer J
Whitehead E, O'Sullivan G, Miller CG. Speed of analgesic onset: placebo-controlled study of ketorolac and two doses of morphine, S323
Whittaker DK, see Keaveny J
Whitten CW, see Gulden RH
Wiesel S
  see Kleiman SJ
  see Kliffer AP
Williamson KA, see Dubbink DA
Williamson WK, Roy RC, Rogers AT, Prough DS, Charles D. Hypercarbia depresses EEG magnitude during cardiopulmonary bypass in man, S324
Winter DC, see Kemmotsu O
Winter E, see Grant GJ
Wiseman E, see MacDonald LE
Withington DE, Elliott ME. Histamine release during paediatric cardiopulmonary bypass, S325
Witkowski TA, see Bartkowski RR
Witt WO, see Walmsley PNH
Woelfel SK, Brandom BW, Sarner JB, Cook DR, Cyran JA. Dose-response of ORG-9426 in children during nitrous oxide-halothane anesthesia, S326
Woltmann A, see Kress HG

Wong SY, see Kwan WF
Wood AJJ, see Deegan R
Wood JR, see Murphy JT
Wood M, see Deegan R
Wright PMC, Carabine UA, Kearney E, Howe JP. Intravenous clonidine: effect on the cardiovascular response to intubation, S327

Yaksh TL
  see Baker AJ
  see Correa-Sales C
Yamamura T, Sato K, Furumido H, Kemmotsu O. Continuous Fick cardiac output measurement during anesthesia, S328
  see Dozaki S
  see Harada K
  see Kemmotsu O
Yamanoue T, Brum JM, Waters V, Ferrario CM, Estafanous FG, Khairallah PA. Effects of opioid anesthetics on porcine coronary artery responses to neurohumoral agents, S329
Yang JT, Brull SJ, Turner J, Connelly NR, O'Connor TZ, Silverman DG. Effect of succinylcholine on the rate and nature of recovery from nondepolarizing blockade, S330
Yang M-W, see Lin CY
Yasuda N
  see Kondo T
  see Toriumi K
Yee R
  see Dobkowski WB
  see Sharpe MD
Yemen T, see Pilato MA
Yokoyama M, Ueda W, Hirakawa M, Goto H, Arakawa K. Effect of epinephrine on lidocaine induced convulsion in rats, S331
Yoon H, see Tetzlaff JE
Young LV, see Roa NL
Young P, see Teasdale S
Youngberg JA, see Meyer P
Yuvorek G, see Patel N

Zacny JP, see Dohrn CS
Zakowski M, Ramanathan S, Khoo P, Turndorf H. Pharmacokinetics of two-dose epidural morphine regimen for cesarean section analgesia, S332
Zaune U, Spies C, Pauli HMF, Boeden G, Martin E. Monitoring of the oxygen utilization by dual oximetry during aortic surgery, S333
  see Spies C
Zavisca F, Heavner J, Kytta J, Rosenberg P Iacono C, Badgwell M. Bupivacaine toxicity in spontaneously hypertensive rats, S334
  see Heavner J
Zelcer J, White PF, Paull JP, Chester S. Intraoperative alfentanil PCA: comparison with standard bolus and infusion techniques, S335
Zhang X, see Waxler B
Zornow MH, see Baker AJ
Zung N, see Shibutani K
Zwass M, see Welborn L

Subject Index

- **Adenosine**
  - see Anesthetic techniques, hypotensive
  - see Neuromuscular transmission
  - see Receptors
- **Age factors**
  - outcome
    - craniotomy, S154
  - resuscitation
    - of elderly, S59
- **Alfentanil,** see Analgesics
- **Ambulatory,** see Anesthesia, outpatient
- **Aminophylline,** see Pharmacology
- **Analgesics**
  - alfentanil
    - methohexital associated jerky movements and cough effects, S137
    - muscle rigidity, kappa agonist antagonism of, S319
    - outpatient, hemodynamics, emergence and recovery, desflurane compared to, S14
    - patient-controlled analgesia, intraoperative, S335
    - pediatric, continuous infusion, S93
    - pediatric, hemodynamic responses and recovery, S193
    - propofol hypnotic effects and, S308
  - buprenorphine
    - pediatric, sacral epidural, efficacy, morphine compared to, S300
    - postcesarean section, morphine compared to, S31
  - butorphanol
    - pediatric, day-care, S202
    - postanesthesia shaking effects, meperidine, morphine compared to, S310
  - fentanyl
    - intrathecal, labor, sufentanil compared to, S159
    - intrathecal, persistent low back pain evaluation and, S124
    - neuroanesthesia, sufentanil, isoflurane compared to, S210
    - pediatric, thiopental requirements effects, S272
    - potency, pentamorphone compared to, S113
    - respiratory depression, S17
  - ketorolac
    - onset, speed of, S323
  - meperidine
    - intrathecal, labor, efficacy, S287
    - postanesthesia shaking effects, butorphanol, morphine compared to, S310
  - morphine
    - onset, speed of, S323
    - patient-controlled analgesia and, S123
    - pediatric, sacral epidural, efficacy, buprenorphine compared to, S300
    - postanesthesia shaking effects, butorphanol, meperidine compared to, S310
    - postcesarean section, buprenorphine compared to, S31
  - ocfentanil
    - balanced anesthesia, fentanyl compared to, S242
    - postoperative, multiple dose evaluation, S63
  - pentamorphone
    - hemodynamic effects, for cardiac anesthesia, S71
    - potency, fentanyl compared to, S113
  - sufentanil
    - accessory pathway conduction, in Wolff-Parkinson-White syndrome, S248
    - intrathecal, labor, fentanyl compared to, S159
    - neuroanesthesia, fentanyl, isoflurane compared to, S210
    - spinal, potentiation of, hydroxypropyl-B-cyclodextrin and, S180
- **Anesthesia**
  - cardiovascular
    - anesthetic agents, propofol-sufentanil vs enflurane-sufentanil, S98
    - aortic aneurysm, cerebrospinal fluid drainage and, S249
    - aortic cross-clamping, blood pressure changes, S250
    - body temperature, S28
    - butanedione, cardiac function and rhythm effects, after hyperperfusion, S23
    - cardiopulmonary bypass, cerebral blood flow, transcranial Doppler verification of, S194
    - coronary artery bypass, CPK-MB levels, steroid effects on, S170
    - coronary artery bypass, hypertension, myocardial oxygenation and ischemia in, S195
    - coronary artery bypass, ischemia, nitroglycerin effects on, S164
    - postoperative myocardial ischemia, diltiazem vs nitroprusside, S294
  - drugs used, nonanesthesiologist and, S37
  - electroconvulsive therapy
    - hemodynamic response, esmolol and labetalol effects on, S224
    - vasopressin release, with catecholamines, S264
  - neurosurgical
    - craniotomy, awake, narcotic use and, S91
    - craniotomy, outcome, age factors, S154
    - emergence, brain tumor size and location and, S237
    - neuroradiology, S169
  - obstetric
    - cesarean section, fentanyl, epidural vs intravenous, S92
    - cesarean section, lidocaine, opioids added to, S149
    - cesarean section, opioids, added to lidocaine, S149
    - epidural, catheters, lidocaine test dose and fentanyl effects, S65
    - epidural, vaginal delivery, primiparous parturient, S35
  - ophthalmologic
    - strabismus, retrobulbar compared to general anesthesia, S38
  - otolaryngolic
    - myocardial ischemia detection during, S205
  - outpatient
    - discharge criteria, S42
  - pediatric
    - alfentanil, continuous infusion, S93
    - blood pressure, monitoring, arterial tonometry for, S135
    - brain laryngeal mask airway, S220
    - caudal, epinephrine, voiding effects, S73
    - neostigmine, neuromuscular blockade, S21
    - outpatient, cardiovascular complications, S136
    - outpatient, hematocrit prior to, S12
    - outpatient, premedication, oral midazolam compared to rectal methohexital, S214
    - parental presence, S16
    - vecuronium, tracheal intubation, S138
  - preoperative laboratory tests, S183
  - thoracic
    - one-lung ventilation, different anesthetic regimens in, S270
    - one-lung ventilation, endobronchial intubation, S34
    - one-lung ventilation, single-lumen tube for, S64
    - respiratory monitoring, preoperative, S200
  - trauma
    - anergy and, S146
  - urologic
    - nephrolithotomy, bupivacaine, S232
- **Anesthetic depth,** see Measurement techniques
- **Anesthetic techniques**
  - epidural
    - blood coagulation delay and, S117
    - catheter aspirate, CSF in, distinguished from local anesthetic, pentothal test for, S317
    - caudal, epinephrine, voiding effects, in children, S73
    - EDTA, tetanic contractions and, S312

    - morphine, cesarean section, two-dose, pharmacokinetics, S332
    - obstetric, vaginal delivery, primiparous parturient, S35
    - recovery, S311
    - sedation during, methohexital and, S6
    - sedation during, midazolam and, S6
    - sedation during, propofol and, S6
    - spread, positioning and obesity effects on, S185
    - sufentanil, pain relief, bupivacaine and, S307
    - tremor patterns, electromyographic analysis of, S245
    - vascular surgery, improved outcome, S302
  - hypotensive
    - adenosine triphosphate, cardiovascular and respiratory function effects, S132
    - esmolol, nitroprusside compared to, S22
    - nicardipine, cardiovascular hemodynamics effects, nitroprusside compared to, S72
    - nitroprusside, esmolol compared to, S22
    - prostaglandin E1 and, S52
    - renal function analysis during, S53
    - ST segment analysis during, S44
  - oral
    - clonidine, tetracaine spinal anesthesia duration and, S204
  - regional
    - brachial plexus, mepivacaine, S225
    - brachial plexus, renal failure, S186
    - drug combinations, S40
    - interscalene block, patient acceptance, S295
    - radiologic techniques, S125
    - sphenopalatine block, lidocaine, intranasal, ischemic tourniquet pain effects, S269
  - spinal
    - continuous, lithotripsy, 32 gauge catheter, S231
    - fentanyl/lidocaine, postoperative analgesia, S20
    - headache, 27 gauge Sprotte and 27 gauge Quincke needles and, S75
    - headache, incidence, S190
    - headache, paramedian approach and, S131
    - lidocaine/fentanyl, postoperative analgesia, S20
    - subarachnoid space, local anesthetic, spread of hyperbaric and isobaric solutions, needle vs catheter, S336
- **Anesthetics, gases**
  - nitrous oxide
    - abuse potential, S51
    - contractility and O_2 utilization effects, in guinea pig hearts, N_2O, isoflurane compared to, S280
    - negative inotropic effects, transsarcolemmal Ca^{2+} entry and, S32
  - wasted
    - costs of, S151
- **Anesthetics, intravenous**
  - droperidol
    - ephedrine renal effects and, S128
  - etomidate
    - cardiac effects, ketamine, midazolam, propofol and thiopental compared to, S281
    - cardioversion, hemodynamic response to, methohexital compared to, S197
    - sympathetic neural outflow and baroreflex function effects, propofol compared to, S61
  - ketamine
    - cardiac effects, etomidate, midazolam, propofol and thiopental compared to, S281
    - positive inotropic effects, S46
  - methohexital
    - cardioversion, hemodynamic response, etomidate compared to, S197
  - opioids
    - coronary artery responses to neurohumoral agents effects, S329
  - propofol
    - auditory evoked potentials, neuronal oscillations effects, S241
    - awakening rates, S5
    - cesarean section, fetoplacental circulation effects, thiopentone compared to, S206
    - esmolol, alfentanil effects during, S306
    - hemodynamic response, glycopyrrolate and, S262
    - mental recovery parameters, isoflurane compared to, S167
    - pediatric, postoperative vomiting effects, S316
    - recovery, desflurane compared to, S163
    - recovery, epidural anesthesia and, S6
    - sedative, amnestic, and anxiolytic effects, S188
    - sympathetic activity effects, norepinephrine kinetics and, S49
    - sympathetic neural outflow and baroreflex effects, etomidate compared to, S61
    - total, without nitrous oxide or narcotic infusion, S255
  - thiopental
    - cardiac effects, etomidate, ketamine, midazolam compared to, S281
    - cesarean section, fetoplacental circulation effects, propofol compared to, S206
- **Anesthetics, local**
  - bupivacaine
    - cardiovascular and central nervous system effects, magnesium deficiency and, S103
    - interpleural, plasma levels, in elderly, S140
    - toxicity, in spontaneously hypertensive rats, S334
  - lidocaine
    - convulsions, epinephrine effects on, S331
  - tropacocaine derivatives
    - muscarinic receptor subtype selectivity S97
- **Anesthetics, volatile**
  - desflurane
    - awakening rates, S5
    - coronary artery bypass, hemodynamic effects, isoflurane compared to, S271
    - emergence from, isoflurane compared to, S150
    - hemodynamic responses to, isoflurane compared to, S13
    - in elderly, isoflurane compared to, S19, S179
    - myocardial contractility effects, isoflurane compared to, S207
    - neuromuscular function effects, isoflurane compared to, S88
    - outpatient, hemodynamics, emergence and recovery, alfentanil compared to S14
    - outpatient, psychomotor recovery after S78
    - pediatric, halothane compared to, S320
    - recovery, isoflurane compared to, S299
    - recovery, propofol compared to, S163
    - vecuronium-induced neuromuscular blockade effects, S89
  - enflurane
    - AV conduction and accessory pathway effects, S50
    - cardiac length-tension relation effects, in ferret, S8
    - ischemia and reperfusion effects, S30
    - mesenteric vein contractile activity effects, S274
    - potassium current in Purkinje cells effects, S286
  - halothane
    - cardiac length-tension relation effects, in ferret, S8
    - cardiovascular effects, age factors, S176
    - dose response curve, cardiopulmonary bypass and, S268
    - leukotriene-D4 induced constriction of guinea pig trachea, attenuation of, S301
    - norepinephrine conduction velocity effects and, S303
    - pediatric, cardiovascular depression, isoflurane compared to, S196
    - pediatric, cerebrovascular response to carbon dioxide effects, S161
    - pediatric, desflurane compared to, S320
    - potassium current in Purkinje cells effects, S286
    - proto-oncogene 'c-myc' expression and, S84
    - sodium channel currents effects, S69
    - synaptic mechanisms, S101
  - isoflurane
    - calcium-dependent sympathetic

      - ganglionic transmission effects, S234
    - cardiac length-tension relation effects, in ferret, S8
    - cardiovascular effects, age factors, S177
    - coronary artery bypass, hemodynamic effects, desflurane compared to, S271
    - depth, inspiratory effort and, S279
    - hemodynamic responses to, desflurane compared to, S13
    - in elderly, desflurane compared to, S19
    - inhalational induction, S178
    - leukotriene-D4 induced constriction of guinea pig trachea, attenuation of, S301
    - mesenteric vein contractile activity effects, S274
    - methylcholanthrene-induced rat sarcoma growth effects, S87
    - myocardial contractility effects, desflurane compared to, S207
    - neuromuscular function effects, desflurane compared to, S88
    - norepinephrine conduction velocity effects and, S303
    - pediatric, cardiovascular depression, halothane compared to, S196
    - pediatric, cerebrovascular hysteresis, halothane compared to, S160
    - potassium current in Purkinje cells effects, S286
    - prolonged anesthesia, serum fluoride effects, sevoflurane compared to, S298
    - recovery, desflurane compared to, S299
    - recovery, parameters, propofol compared to, S167
    - unconscious learning and, S60
    - vasodilation effects, S48
  - sevoflurane
    - prolonged anesthesia, serum fluoride effects, isoflurane compared to, S298
    - serum inorganic fluoride levels effects, in anuric patients, S141

- **Antagonists, benzodiazepines**
  - flumazenil, midazolam-induced ventilatory depression, S322
- **Antagonists, neuromuscular relaxants**
  - neostigmine
    - pediatric, S21
- **Antiemetics,** see Vomiting
- **Aortic aneurysms,** see Anesthesia, cardiovascular
- **Aortic cross-clamping,** see Anesthesia, cardiovascular
- **Aspiration,** see Complications
- **Asthma,** see Complications
- **Ataractic agents**
  - MAO inhibitors
    - discontinuation of, preoperative, S62
- **Atracurium,** see Neuromuscular relaxants

- **Benzodiazepines,** see Hypnotics
- **Blood**
  - coagulation
    - assessment, thromboelastogram, S313
    - cardiac surgery, antithrombin III-heparin complex and activated clotting time relationship, S120
    - cardiac surgery, cardiopulmonary bypass, S121
    - heparin, coronary bypass surgery, S143
    - measurement, intraoperative, laser photometer, S201
  - hematocrit
    - pediatric, S12
  - hemodilution
    - oxygen delivery effects, S304
  - hemoglobin
    - modifications, S252
  - platelets
    - in shed mediastinal blood, autotransfusion and, S142
    - receptors, loss, cardiopulmonary bypass and, S223
- **Blood-brain barrier,** see Brain
- **Brachial plexus**
  - see Anesthetic techniques, regional
  - see Nerve
- **Brain**
  - blood flow
    - cardiopulmonary bypass, anesthetic technique effects on, S221
    - fenoldopam effects on, S106
    - hysteresis, pediatric, isoflurane, halothane compared to, S160
    - serotonin effects, volatile anesthetics and, S79
  - blood-brain barrier
    - permeability, following ischemia, pentastarch effects on, S235
  - edema
    - post-traumatic, methylprednisolone and, S247
  - evoked potentials
    - cortical, magnetically induced, hypothermia effects on, S260
    - cortical, magnetically induced, ventilation alterations effects on, S261
  - ischemia
    - protection, S112, S114
- **Breathing,** see Ventilation
- **Bupivacaine,** see Anesthetics, local
- **Buprenorphine,** see Analgesics
- **Butanedione,** see Anesthesia, cardiovascular
- **Butorphanol,** see Analgesics

- **Calcitonin,** see Polypeptides
- **Calcium channel blockers,** see Pharmacology
- **Carbon dioxide**
  - hypercarbia
    - during cardiopulmonary bypass, EEG changes, S324
- **Cardiac output,** see Measurement techniques
- **Cardiopulmonary bypass**
  - see Surgery, cardiovascular
  - see Temperature, body
- **Cardiovascular anesthesia**
  - see Anesthesia
  - see Surgery, cardiovascular
- **Carotid artery,** see Surgery, vascular
- **Catecholamines**
  - see Hypothermia
  - see Sympathetic nervous system
- **Caudal,** see Anesthetic techniques, epidural
- **Cesarean section,** see Anesthesia, obstetric
- **Children,** see Anesthesia, pediatric
- **Cholecystectomy,** see Surgery
- **Clonidine**
  - see Anesthetic techniques, oral
  - see Intubation, tracheal
  - see Sympathetic nervous system, pharmacology
- **Clotting,** see Blood, coagulation
- **Coagulation,** see Blood
- **Complications**
  - aspiration
    - prevention, famotidine, ranitidine, S246
  - asthma
    - epidural anesthesia and analgesia and, S292
  - hypotension
    - intraoperative, risk factors, S148
  - intraoperative
    - rates, S116
  - postoperative
    - narcotics, intravenous and epidural, S189
    - pulmonary, enflurane, isoflurane comparisons, S315
  - shivering
    - nonshivering thermogenesis, absence of, S119
  - tobacco smoking
    - patient duration in post anesthesia care unit and, S99
- **Continuous positive pressure breathing, see Ventilation**
- **Coronary artery bypass graft,** see Anesthesia, cardiovascular
- **CPPB,** see Ventilation, continuous positive pressure breathing
- **Cuffs,** see Equipment

- **Denitrogenation,** see Induction, anesthesia
- **Desflurane,** see Anesthetics, volatile
- **Dexmedetomidine**
  - see Premedication
  - see Sympathetic nervous system, pharmacology
- **Dextran,** see Fluid balance
- **Diaphragm,** see Muscle, skeletal
- **Diazepam,** see Hypnotics, benzodiazepines
- **Droperidol**
  - see Anesthetics, intravenous
  - see Vomiting, antiemetics

- **Echocardiography,** see Measurement techniques
- **Edema,** see Brain
- **Education**
  - examinations
    - oral, S238

  - residents
    - competence criteria, S86
    - selection, S82
- **Electrocardiography,** see Heart
- **Electroconvulsive therapy,** see Anesthesia
- **Emboli,** see Measurement techniques
- **Emphysema,** see Lung
- **End-tidal CO_2,** see Measurement techniques
- **Endotoxin,** see Shock
- **Endotracheal**
  - see Equipment, tubes, tracheal
  - see Intubation, tracheal
- **Enflurane,** see Anesthetics, volatile
- **Enzymes**
  - proteinase
    - inhibitors, anesthetics effects on, S318
- **Epidural,** see Anesthetic techniques
- **Equipment**
  - cuffs
    - endotracheal, laser ignition, prevention, S266
    - endotracheal, leaks, sealability, temperature and dilution effects on, S239
  - lasers
    - protective devices, S265, S266
  - needles
    - spinal, 24 gauge Sprott, 27 gauge Quincke, post dural puncture headache effects, S75
  - tourniquets
    - pediatric, fever induction, S191
    - pneumatic, ECG and blood gas changes with, S70
  - tubes
    - endotracheal, KTP laser and, protection, S267
  - ventilators
    - bellows leaks effects on, S215
  - warming devices
    - comparisons, S118
- **Esmolol**
  - see Anesthetic techniques, hypotensive
  - see Sympathetic nervous system, pharmacology
- **Esophagus,** see Gastrointestinal tract
- **Etomidate,** see Anesthetics, intravenous
- **Evoked potentials,** see Brain
- **Examinations,** see Education

- **Fenoldopam,** see Brain, blood flow
- **Fentanyl,** see Analgesics
- **Fluid balance**
  - saline and dextran, S209
- **Flumazenil,** see Antagonists, benzodiazepines
- **Fluoride,** see Ions

- **Gastrointestinal tract**
  - esophagus
    - contractility, post anesthesia recovery room complications reduction and, S110
  - stomach
    - omeprazole, gastric volume and acidity effects, S102
- **Genetics,** see Potency, anesthetic

- **Halothane,** see Anesthetics, volatile
- **Headache,** see Anesthetic techniques, spinal
- **Heart**
  - blood flow
    - myocardial, subarachnoid hemorrhage and ECG abnormalities and, S289
  - coronary occlusion
    - isoflurane, adenosine and, S314
  - electrocardiography
    - prone position effects on, S168
  - ischemia
    - epidural anesthesia and, S15
    - intraoperative, ECG comparisons, S126
  - Purkinje fibers
    - inhalation anesthetics effects on, S152, S153
  - tamponade
    - left ventricular transmural pressure monitoring, S203
- **Hematocrit,** see Blood
- **Hemodilution,** see Blood
- **Hemoglobin,** see Blood
- **Hemorrhage,** see Shock
- **Heparin,** see Blood, coagulation
- **High frequency jet ventilation,** see Ventilation
- **Histamine**
  - ranitidine
    - during anesthesia, gastric pH and volume effects, S155
    - nausea and vomiting effects, after propofol-isoflurane anesthesia, S145
  - release
    - during cardiopulmonary bypass, pediatric, S325
- **Hypercarbia,** see Carbon dioxide
- **Hypnotics**
  - benzodiazepines
    - midazolam, during monitored anesthesia care, propofol with, S293
    - midazolam, levels, in cardiopulmonary circuit, S133
    - midazolam, pediatric, premedication, S297
- **Hypotension,** see Anesthetic techniques, hypotensive
- **Hypothermia**
  - brain protection, ischemia and, S9
  - catecholamines
    - cardiac effectivity effects, S104
  - evoked potentials effects, S260
- **Hypoxia**
  - nicardipine, protective effects, S83

- **Immune responses**
  - T-cell
    - volatile anesthetics effects on, S173
- **Induction**
  - anesthesia
    - denitrogenation, vital capacity breathing during, S182
    - preoxygenation, time, anthropometric and pulmonary variables and, S288
- **Infection**
  - prevention, S228
  - upper respiratory tract
    - tracheal intubation and, S291
- **Intensive care**
  - readmissions, S58
- **Interpleural,** see Pain, postoperative
- **Interscalene block,** see Anesthetic techniques, regional
- **Intubation**
  - reintubation
    - emergent, in postanesthesia recovery room, S157
  - tracheal
    - clonidine, cardiovascular responses, S327
    - fiberoptic, patient position assessment, S253
    - responses to, hemodynamic, neuromuscular blockade and, S90
    - responses to, tachycardia and hypertension, lidocaine, fentanyl and esmolol effects on, S105
    - semi-emergent, patient outcome and anesthesia care during, S74
    - tube diameter, pediatric, estimation of, S85
- **Ions**
  - fluoride
    - plasma and urinary levels, toxic, urinary PGE2 and, S3
- **Isoflurane,** see Anesthetics, volatile
- **Isoproterenol,** see Sympathetic nervous system, pharmacology

- **Ketamine,** see Anesthetics, intravenous
- **Ketanserine,** see Pharmacology
- **Ketorolac,** see Analgesics

- **Lasers,** see Equipment
- **Lithotripsy**
  - see Anesthesia, urologic
  - see Anesthetic techniques, spinal, continuous
- **Lung**
  - emphysema
    - bullous, laser treatment, S11
  - pulmonary function
    - postoperative, pain scores and, S18
  - vascular resistance
    - direct measurement of, S108

- **MAO inhibitors,** see Ataractic agents
- **Masseter muscle,** see Muscle, skeletal
- **Measurement techniques**
  - anesthetic depth
    - inspiratory effort, S171
  - blood pressure
    - arterial, low pass filtering, S212
  - cardiac output
    - Fick equation, S328
  - echocardiography
    - contrast, cardioplegic, in aortic regurgitation, S217

    contrast, tricuspid regurgitation estimation, S219
    spinal cord imaging with, S67
    transesophageal, aortic annulus measurement, S165
    transesophageal, pediatric, of congenital heart defects, S192
  emboli
    micro, cardiopulmonary bypass, S277
  end-tidal CO_2, S251
    pediatric, low fresh gas flows and volume-cycled ventilators effects on, S273
  neuromuscular
    50 Hz tetany, train-of-four compared to, S278
  oximetry
    dual, S333
    failure, reversal of, by digital nerve block, S81
  pulmonary capillary pressure
    arterial occlusion pressure curve and, S216
  transducers
    pressure, performance, inside magnetic resonance imaging scanner, S109
Meperidine, see Analgesics
Methohexital, see Anesthetics, intravenous
Metoclopramide, see Vomiting, antiemetics
Metoprolol, see Sympathetic nervous system, pharmacology
Midazolam, see Hypnotics, benzodiazepines
Monitoring
  during MRI, S130
  quality assurance, S213
Morphine
  see Analgesics
  see Pain, chronic
Muscle
  skeletal
    diaphragm, single twitch stimulation, phrenic artery blood flow during, S68
    masseter, spasm, S127

Naproxen, see Pain, postoperative
Needles, see Equipment
Neostigmine, see Antagonists, neuromuscular relaxants
Nephrolithotomy, see Surgery, urologic
Nerve
  brachial plexus
    neurostimulation, S222
Neuromuscular relaxants
  atracurium
    pediatric, low dose, intubation, S174
    pediatric, potency, vecuronium compared to, S259
    pharmacodynamics, vecuronium compared to, S77
  ORG 9426
    effects, enflurane and, S57
    pediatric, potency, vecuronium compared to, S326
    pharmacokinetics, onset and duration of action, renal failure and, S290
  pipecuronium
    in elderly, pharmacokinetics and pharmacodynamics, S172
  pre-curarization
    cesarean section, postoperative myalgia effects, S283
  succinylcholine
    plasma potassium effects, age and, S4
    recovery from nondepolarizing blockade effects, S330
    vecuronium-induced neuromuscular blockade recovery and, S111
  vecuronium
    pediatric, low dose, intubation, S174
    pediatric, potency, atracurium compared to, S259
    pediatric, tracheal intubation, S133
    pharmacodynamics, atracurium compared to, S77
    pharmacokinetics, long-term administration and, S244
Neuromuscular transmission
  adenosine, S80
  measurement
    50 Hz tetany, train-of-four compared to, S278
Neuropsychologic defects, see Surgery, cardiovascular
Neurosurgery, see Anesthesia
Nicardipine, see Hypoxia
Nifedipine, see Pharmacology, calcium blockers
Nitroprusside, see Anesthetic techniques, hypotensive
Nitrous oxide, see Anesthetics, gases

Obstetric, see Anesthesia
Ocfentanil, see Analgesics
Omeprazole, see Gastrointestinal tract, stomach
Ondansetron, see Vomiting, antiemetics
Ophthalmologic, see Anesthesia
ORG 9426, see Neuromuscular relaxants
Otolaryngolic, see Anesthesia
Outpatient, see Anesthesia
Oximetry, see Measurement techniques

PAC, see Pain, patient-controlled analgesia
Pain
  chronic
    management, nerve block and, S100
    morphine, intrathecal, outpatient, S156
  low back
    persistent, evaluation of, intrathecal fentanyl and, S124
    therapies, S45
  measurement
    pediatric, S199
  postoperative
    analgesia, patterns of, S284
    fentanyl, transdermal, hysterectomy, S233
    iliac crest wound perfusion for, S29
    interpleural techniques, in elderly, S139
    interpleural techniques, in elderly, bupivacaine, S140
    naproxen, laparoscopic tubal ligation, S227
    ocfentanil, multiple dose evaluation, S63
    patient-controlled analgesia, S27, S33
    patient-controlled analgesia, intrathecal morphine and, S123
    patient-controlled analgesia, metoclopramide, S229
    patient-controlled analgesia, orthopedic surgery, basal infusion and, S256
    thoracotomy, cryoanalgesia versus intrapleural analgesia, S184
    tonsillectomy, infiltration anesthesia effects, S129
Patient-controlled analgesia, see Pain, postoperative
PCA, see Pain, postoperative
Pediatric, see Anesthesia
PEEP, see Ventilation
Pentamorphone, see Analgesics
Pericardectomy, see Surgery, cardiovascular
Peridural, see Anesthetic techniques, epidural
Pharmacology
  aminophylline
    diaphragmatic fatigue and, S26
  calcium channel blockers
    nifedipine, post-ischemia myocardial blood flow effects, S36
    verapamil, protective effects on left ventricular pressure and ventricular fibrillation, halothane and, S181
  ketanserine
    postoperative hypertension, S305
Phenylephrine, see Sympathetic nervous system, pharmacology
Pipecuronium, see Neuromuscular relaxants
Platelets, see Blood
Polypeptides
  calcitonin, neuromuscular function effects, S76
  substance P
    afferent synaptic responses, propofol and, S275
Positive end expiratory pressure, see Ventilation
Potency, anesthetic
  genetics, S243
Pre-curarization, see Induction, anesthesia
Premedication
  dexmedetomidine
    for laparoscopy, S2
  intravenous
    droperidol, pediatric, pharmacokinetics, S94
  meperidine-midazolam
    pediatric, S321
  midazolam-meperidine
    pediatric, S321

- **Propofol,** see Anesthetics, intravenous
- **Pulmonary capillary pressure,** see Measurement techniques
- **Pulse oximetry,** see Monitoring
- **Purkinje fibers,** see Heart

- **Quality assurance,** see Monitoring

- **Ranitidine**
  - see Histamine
  - see Vomiting
- **Receptors**
  - adenosine
    - acetylcholine release effects, S309
  - opioid
    - antinociceptive effects, in inflamed tissue in rat, S276
- **Records**
  - anesthesia
    - automated, S296
- **Residents,** see Education
- **Resuscitation,** see Age
- **Risk**
  - cardiac, S107

- **Saline,** see Fluid balance
- **Sevoflurane,** see Anesthetics, volatile
- **Shivering,** see Complications
- **Shock**
  - endotoxin
    - Ringer's acetate or dextran 70, S147
  - hemorrhagic
    - epidural/general anesthesia and, S263
- **Smoking,** see Complications
- **Spinal,** see Anesthetic techniques
- **Stellate ganglion,** see Sympathetic nervous system
- **Subarachnoid space,** see Anesthetic techniques, spinal
- **Substance P,** see Polypeptides
- **Succinylcholine,** see Neuromuscular relaxants
- **Sufentanil,** see Analgesics
- **Surgery**
  - cardiovascular
    - cardiopulmonary bypass, pH management and perfusion during, renal function and, S7
    - cardiopulmonary bypass, vasodilator requirements, radiant heat effects on, S95
    - neuropsychological defects, S282
    - pericardectomy, right ventricular dynamics effects, S218
  - carotid endarterectomy
    - microemboli detection, S277
  - cholecystectomy
    - postoperative ventilation, S211
  - transplantation
    - liver, blood loss during, S24
    - liver, blood loss during, thromboelastography and, S25
    - liver, calcium chloride requirements, fresh frozen plasma and, S56
    - liver, hepatic cells, tissue-type plasminogen activator binding with, S134
    - liver, intraoperative blood usage, pseudocholinesterase levels and, S55
  - vascular
    - carotid artery, endarterectomy, EEG-quantified anesthesia, S187
- **Sympathetic nervous system**
  - catecholamines
    - levels, enalaprilat and, S236
  - pharmacology
    - clonidine, endotracheal intubation and, S327
    - clonidine, ischemia and, S39
    - dexmedetomidine, S47
    - dexmedetomidine, cortisol and β-endorphin responses to intubation and laparoscopy effects, S158
    - dexmedetomidine, prazosin effects on, S96
    - esmolol, succinylcholine hemodynamics and intraocular pressure effects and, S144
    - isoproterenol, myocardial ischemia effects, S115
    - metoprolol, post-ischemia myocardial blood flow effects, S36
    - phenylephrine, myocardial O_2 effects, isoflurane-induced hypotension and, S1
  - stellate ganglion
    - ablation, S254

- **T cell,** see Immune response
- **Tamponade,** see Heart
- **Temperature**
  - body
    - cardiopulmonary bypass and, S28
    - cardiopulmonary bypass and, sweating threshold, S258
    - intraoperative, conservation, T-727
      - thermal fabric head covering, S166
    - intraoperative, insulation, S175
    - postoperative, vasoconstriction and, S66
- **Thiethylperazine,** see Vomiting, antiemetics
- **Tonsillectomy,** see Pain, postoperative
- **Tourniquets,** see Equipment
- **Transducers,** see Measurement techniqu
- **Transfusion**
  - autologous, S257
- **Transplantation,** see Surgery
- **Tropacocaine,** see Anesthetics, local
- **Tubes,** see Equipment

- **Urologic,** see Anesthesia

- **Vecuronium,** see Neuromuscular relaxan
- **Ventilation**
  - continuous positive pressure
    - work of breathing calculation, S10
  - high frequency jet
    - hemodynamic and respiratory effect S198
  - positive end expiratory pressure
    - one lung ventilation, PaO_2, SVO_2 effects, S43
  - work of breathing
    - during general anesthesia, S41
    - heat and moisture exchangers effect on, S226
- **Ventilators,** see Equipment
- **Verapamil,** see Pharmacology, calcium blockers
- **Vomiting**
  - antiemetics
    - droperidol, efficacy, metoclopramid compared to, S208
    - droperidol, thiethylperazine compar to, S122
    - metoclopramide, efficacy, droperido compared to, S208
    - ondansetron, S230
    - ondansetron, recovery time effects, S162
    - thiethylperazine, droperidol compar to, S122
  - postoperative
    - in children, gastric suction effects, S240
    - outpatient anesthesia, placebo, ephedrine, antiemetics effects, S28
  - ranitidine effects,, S145

- **Warming devices,** see Equipment

IARS

NEW OFFICE ADDRESS

Effective October 1, 1990, the **International Anesthesia Research Society** headquarters office in Cleveland moved to the following new address:

International Anesthesia
Research Society
Suite 140, 2 Summit Park Drive
Cleveland, Ohio 44131-2553

NEW TELEPHONE NUMBER:
(216) 642-1124

All membership payments and correspondence regarding **IARS** member subscriptions, annual scientific meeting matters, the B.B. Sankey Anesthesia Advancement Award, etc., should be sent to the above address.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
65th CONGRESS — March 8–12, 1991
Marriott Rivercenter ◦ San Antonio, Texas

MEETING REGISTRATION, HOTEL RESERVATION, SCIENTIFIC MEETING INFORMATION: Will be mailed in December to all IARS members. (IARS members outside of North America who plan to attend the meeting will receive this material by airmail upon request.) Non-IARS members should request information from the **NEW IARS OFFICE ADDRESS:** Suite 140, 2 Summit Park Drive, Cleveland, OH 44131. Tel: (216) 642-1124.

MEETING SCHEDULE: **Registration:** Friday, March 8, 1–6 PM
Scientific Program: Saturday–Tuesday, March 12
Exhibits: Saturday–Monday, March 11

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture, Sunday, March 10,
"Anesthesia Journals: The Backbone of the Specialty — Past, Present, and Future"
Nicholas M. Greene, MD, Emeritus Professor of Anesthesiology,
Yale University School of Medicine, New Haven, Connecticut,
and Editor-in-Chief, *ANESTHESIA and ANALGESIA*

REVIEW COURSE LECTURES:

MD Abel, MD	— Transesophageal Echocardiography — Its Real Role in Clinical Anesthesia
PG Barash, MD	— Preoperative Assessment of the Patient With Cardiac Disease
DR Bevan, MD, and RD Miller, MD	— Anesthesia Literature — A Critical Approach to Reading and Writing
DR Cook, MD	— Anesthetic Management of Neonatal and Infant Surgical Emergencies
MJ Cousins, MD	— The Injury Response and the Prevention of Postoperative Pain
BG Covino, MD	— New Techniques in Regional Anesthesia
N Ellison, MD	— Blood Transfusions — When and What?
M Finster, MD	— Newer Trends in Obstetric Pain Relief
AB Froese, MD	— Ventilator-Related Lung Injury — New Concepts
TJ Gal, MD	— Anesthesia and Gas Exchange — HPV, FRC, CC, and Other Acronyms
DE Longnecker, MD	— The Case for Perioperative Blood Pressure Control
M Maze, MD	— Alpha-2 Agonists and Anesthesia
SC Nicolson, MD	— Perioperative Fluid Management in the Pediatric Patient
WS Nimmo, MD	— Alternate Modes of Drug Delivery
GW Ostheimer, MD	— Contemporary Issues in Obstetric Anesthesia
RG Pearl, MD	— Sepsis — Etiology and Management
DS Prough, MD	— Anesthetic Management of the Patient With Head Trauma
C Prys-Roberts, DM	— Total Intravenous Anesthesia — Assessment of Adequacy
JG Reves, MD	— Physiology of Cardiopulmonary Bypass
JJ Savarese, MD	— Does the Choice of Muscle Relaxant Really Matter?
S Slogoff, MD	— Outcome Studies in Anesthetic Data — A Perspective
NT Smith, MD	— Perioperative Anesthetic Data — What to Do With It?
RK Stoelting, MD	— Allergy and Anesthesia
JH Tinker, MD	— How?/Should?/Does? Malpractice Litigation Affect Anesthetic Practice?
PF White, MD	— Monitored Anesthesia Care — Appropriate Use of Adjuvant Drugs
MF Yeager, MD	— The Role of Regional Anesthesia in Improving Surgical Outcome

PANELS

ANESTHESIA MACHINES AND VENTILATORS — Saturday, March 9, 8:00 AM
NW Lawson, MD, Moderator; JJ Andrews, MD, J Condurso, North American Drager, and JB Biondi, Ohmeda

YOU, THE ANESTHESIOLOGIST IN COURT — A MOCK MEDICAL MALPRACTICE TRIAL
(Based on an actual case) — Saturday, March 9, 1:00 PM
DH Morrow, MD, Moderator; Hon. D Hittner, F Stein, MD, TP Sartwelle, Esq., RJ Swift, Esq.

MEDICAL LITIGATION: PROBING THE DEPTHS — Sunday, March 10, 8:00 AM
PG Fine, MD, Moderator; AR Nelson, MD, JA Jacobson, MD, L Andrews, JD

LEGISLATIVE UPDATE — LUNCHEON SESSION — Sunday, March 10
BP Stephenson, MD, and AC Lang, representing American Society of Anesthesiologists

EMERGENCY AIRWAY MANAGEMENT — Monday, March 11, 8:00 AM
MS Gorback, MD, Moderator; JL Benumof, MD, EJ Krane, MD, CB Watson, MD

CLINICAL AND RESEARCH PRESENTATIONS

More than 300 clinical and research papers will be presented in concurrent oral and poster sessions.

REGISTRATION • CME CREDIT ◦ AIR TRAVEL • HOTELS

FEES:	IARS Members — $275 ($300 on site)	Non-members — $450 ($475 on site)
	IARS Educational Members — No fee	Non-member residents — $50 (with certification)

CME CREDIT: Category 1 — 27 hours

DELTA SPECIAL AIRFARES: Discounted fares for IARS meeting registrants. For details call 1-800-241-6760, File No. P-0095.

HOTELS: The Marriott Rivercenter will serve as headquarters hotel where all meetings and exhibits will be held. A limited number of additional rooms have been blocked at the St. Anthony. Reservation forms to be included in the December mailing must be used to obtain the discounted rates of IARS meeting registrants.

The

International Anesthesia Research Society

would like to extend

its gratitude to

◆

BURROUGHS WELLCOME CO.

for the educational grant necessary

for the publication of this

◆

Annual Abstract Issue

from its meeting

on March 8–12, 1991

in San Antonio, Texas